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ACUTE ILIAC ADENITIS

REPORT OF EIGHTEEN CASES

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SAN JUAN, PUERTO RICO

Acute iliac adenitis, or inflammation in the iliac lymph glands, presents a clinical picture which is not as uncommon as its lack of recognition would indicate. The disease usually occurs in children or in young adults. It is characterized by a history of cutaneous infection or of trauma of the lower extremity or abdomen which precedes by two or three weeks the appearance of a large, hard, tender, fixed mass in the iliac fossa. There are pain, fever, leukocytosis and spasm of the psoas muscle producing flexion deformity of the thigh.

The purpose of this study is (1) to review the scanty literature, (2) to present the report of a series of 18 cases and (3) to give a clear and comprehensive description of this seldom correctly diagnosed clinical entity.

REVIEW OF THE LITERATURE

Abrille [1] in 1854 reported 8 cases of suppuration in the retroperitoneal tissues. At that time few pathologists had given the subject serious attention. He divided infection of the retroperitoneal space according to frequency into (1) abscess in the iliac fossa, (2) abscess behind the pelvic peritoneum and (3) perinephritic abscess. He had no knowledge of the cause, considering the condition of traumatic or of idiopathic origin. In 1903 Pegram [2] described 2 cases of iliac adenitis as illustrating possible errors in the diagnosis of disease of the hip joint. The two cases he reported were those of a boy of 3 years and a girl of 6 years. Both had pain, fever, leukocytosis, flexion deformity of the thigh and tumor in the left iliac fossa. Both were operated on, and pus was encountered in the iliac glands of both. His is the first

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1. Abrille, C.: Retroperitoneal Abscess, Gaz. d. hôp. **27**:218, 1854.

2. Pegram, J. C.: Report of Two Cases of Suppuration of Retromesenteric Lymph Nodes, Tr. Rhode Island M. Soc. **6**:643, 1903.

complete description of the syndrome. Hamann [3] in 1907 reported 3 cases, the patients being respectively 13, 5 and 2 years of age, in which suppuration started primarily in the iliac glands, giving the typical picture of fever, flexed thigh and mass in the iliac fossa. Huggins [4] reviewed the literature up to 1911 on suppuration in the retroperitoneal space. Of the 8 cases he reported, 2 were instances of the iliac variety.

The syndrome of iliac adenitis is apparently well known in South America. From Argentina, Rivarola [5] in 1924 presented a clear and accurate description of the disease. Lugones [6] in 1926 observed 3 cases in which the condition occurred in children and was metastatic following bronchopneumonia. Coutts [7] in 1927, from Chile, reported 4 cases, in all of which the disease was traceable to preceding infection in the urethra, the prostate or the rectum. Bailey [8] in 1930 published reports of 7 cases, and in 1935 he had observed 5 more. Hyman [9] in 1930 was able to collect data on 21 patients with the condition who had been admitted to Mount Sinai Hospital, New York. Both Bailey [8] and Hyman [9] commented on the scarcity of publications on this subject. Largos García [10] in 1931 reviewed the South American literature, presented 38 cases of his own and admirably summarized the clinical picture. Barbarousse and del Campo [11] in 1933 published in detail the reports of 10 cases from Uruguay. Bose [12] in 1934 recorded 2 cases in which the condition simulated appendicitis. To the records of the 92 cases just mentioned I add the 18 following.

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3. Hamann, C. A.: Suppuration in the Retroperitoneal Glands, Cleveland M. J. **6**:399, 1907.

4. Huggins, R. H.: Suppuration in the Retroperitoneal Space, Surg., Gynec. & Obst. **12**:276 (Feb.) 1911.

5. Rivarola, R. A.: Adenitis iliacas agudas, Bol. y trab. de la Soc. de cir. de Buenos Aires **8**:195, 1924.

6. Lugones, C.: Adenitis agudas de los ganglios iliacos, Rev. méd. latino-am. **11**:124 (Jan.) 1926.

7. Coutts, W. E.: Acute Inflammation of Deep Iliac Lymph Nodes, Rev. Soc. urol. de Chile **9**:268 (Nov.) 1926.

8. Bailey, H.: Suppurating Deep Iliac Glands, Practitioner **124**:223 (Feb.) 1930.

9. Hyman, A.: Suppurative Retroperitoneal Pelvic Lymphadenitis, Ann. Surg. **91**:718 (May) 1930.

10. Largos García, A.: La adenitis ilíaca aguda, Semana méd. **2**:1160 (Oct. 8) 1931.

11. Del Campo, R. M., and Barberousse, C. M.: Las adenitis iliacas agudas en el niño, Arch. de pediat. d. Uruguay **4**:43 (Feb.) 1933.

12. Bose, M.: Lymphadenitis of the Retroperitoneal Glands Simulating Appendicitis, Indian M. Gaz. **69**:579 (Oct.) 1934.

REPORT OF CASES

CASE 1.—N. D., a boy aged 7 years, was admitted to the hospital in March 1934, with a history of pain in the right lower quadrant of the abdomen, fever, anorexia and inability to straighten the right leg of thirty days' duration. He had had frequent cutaneous infections for three years. Clinical findings were: temperature 101 F., tachycardia, old impetiginous lesions of the extremities and rigid flexion deformity of the right thigh. The abdomen was soft, allowing a large, hard, tender, fixed mass in the right iliac fossa to be outlined with ease. The tumor extended from the inguinal ligament 7 cm. upward and medially. The inner superior border was rounded and dipped deeply into the abdomen. Results of tuberculin tests and of serologic tests for syphilis were negative; the white cell count was 21,600, and there was mild anemia. Roentgenograms of the spine, pelvis and hip joint showed normal structures. With continuous ice compresses applied over the tumor, forced fluids and general nursing care the fever gradually subsided and the mass and psoas spasm slowly disappeared. The patient was discharged "well" thirty days after admission.

CASE 2.—M. V., a boy aged 10 years, entered the hospital in 1927 complaining of fever and pain in the left side of the abdomen of twenty-seven days' duration. A hard, tender, sharply outlined mass was present deep in the left iliac fossa, extending 5 cm. above the inguinal ligament. All movements of the hip joint were freely elicited except extension. A count of 30,000 leukocytes was observed, and there was moderate secondary anemia. At operation a small abscess was found in the thick-walled tumor and was drained. Staphylococcus aureus haemolyticus was grown from the pus obtained. A section of the wall of the tumor removed for pathologic study was described as retroperitoneal tissue infiltrated with polymorphonuclear leukocytes and round cells. Recovery was uneventful.

CASE 3.—P. L., a boy aged 13, was first admitted to the hospital in November 1932, with a history of fever, pain in the right side and inability to extend the right thigh during the past thirty days. He had sustained an injury to the right groin three years previously, when he was kicked by a horse. He had had repeated cutaneous infections of the feet and legs. His parents had noticed a lump in the right side of the abdomen, which had been slowly increasing in size during the last thirty days prior to admission. Clinical findings of importance were pallor, a temperature of 101 F. and a tender, fixed firm mass in the right iliac fossa. The right thigh was held rigidly flexed on the abdomen and could not be extended. Many scars of old impetiginous lesions were present on the lower extremities. Laboratory examinations revealed: red cell count, 1,440,000; hemoglobin, 38 per cent; white cell count, 18,000; result of serologic test for syphilis, negative. Many hookworm ova were present in the stools. Roentgenograms of the spine and pelvis showed them to be normal. With ice compresses over the tumor, hookworm treatment and correction of anemia the mass slowly disappeared, and the patient was discharged well two months after admission. He returned in August 1935, three years later, with a history for the past eleven days of pain, fever and reappearance of the mass. He had been well during the interim. Clinical findings were identical with those obtained at the first admission. A hard, tender mass again occupied the right iliac fossa (fig. 1). No improvement having been obtained by medical treatment, an incision was made over the mass and the peritoneal cavity was entered. A large hard tumor 5 cm. in diameter filled the right iliac fossa completely. The tumor grossly resembled a sarcoma. It was extraperitonealized and incised. A small quantity of thick green pus was encountered at the center of the abscess, which produced on culture a hemolytic staphylococcus. A fragment

of the wall of the tumor removed for biopsy was described by the pathologist as follows: There was homogeneous grayish white tissue which showed numerous closely packed, medium-sized polygonal cells with pale, vacuolated, acidophilic cytoplasm and prominent oval nuclei. Local hemorrhage and numerous foci of infiltration by polymorphonuclear leukocytes were present. The diagnosis was chronic inflammatory changes (fig. 2). With drainage of the abscess convalescence was rapid, and the boy was discharged twenty days after admission.

CASE 4.—L. A., a girl aged 8 years, was admitted to the hospital in January 1935, complaining of pain in the right lower quadrant of the abdomen, fever and inability to extend the right thigh during the past five days. She had had a chronic vaginal discharge since infancy. Physical examination disclosed a soft abdomen in which could be felt a globular hard, fixed, tender mass, 6 cm. in

Fig. 1 (case 3).—Photograph illustrating spasm of the psoas muscle with flexion of the right thigh. The tumor is visible in the right iliac fossa (upper margin outlined with mercurochrome).

diameter, occupying the right iliac fossa. The right thigh was flexed on the abdomen. A leukocyte count of 21,900, an erythrocyte count of 3,200,000 (indicating secondary anemia) and a hemoglobin content of 59 per cent were observed. A mixed bacterial flora was present in the vaginal smear. No improvement was obtained with local heat. At operation an incision was made above and parallel to the inguinal ligament. A small abscess was found in the iliac glands, and was drained. Staph. aureus haemolyticus was grown from the pus. Recovery was uneventful.

CASE 5.—S. O., a boy aged 4 years, entered the hospital in September 1925. He had had a chronic infection of the upper respiratory tract for two months and pain in the right lower quadrant of the abdomen for two weeks. He had fever and had vomited. Physical examination revealed a feverish sick child with the

right thigh rigidly flexed on the abdomen. A mass was visible in the right iliac fossa, which measured 5 cm. at its greatest diameter. Secondary anemia and a leukocyte count of 20,000 were observed. Roentgenograms of the spine, the pelvis and the hip joints showed no abnormal changes. Incision over the mass disclosed a large, hard tumor with a small abscess cavity at its center. Culture of the pus produced a pneumococcus. Convalescence with drainage was rapid. The patient was discharged well thirty-two days after admission.

The remaining 13 cases are presented in tabular form.

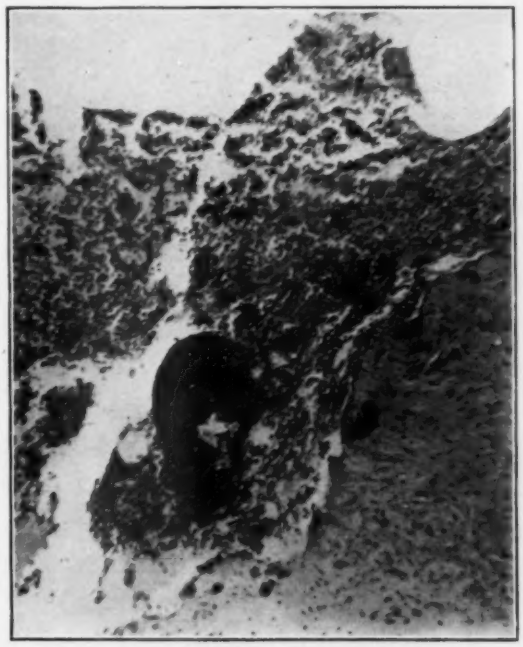

Fig. 2 (case 3).—High power magnification showing a section through the wall of the abscess and the hyperplastic character of the retroperitoneal tissue.

COMMENT

From the histories and clinical findings in the cases reported, certain characteristics of acute iliac adenitis are seen to be present constantly enough to form a syndrome. The vagueness of the symptoms at onset and their resemblance to those of acute appendicitis, disease of the hip joint, osteomyelitis of the head of the femur and abscess of the psoas muscle account for the infrequency of correct diagnosis of the condition.

The abscess occurs in the external iliac lymph glands of either side. These glands are divided into external, middle and internal chains. The external chain is comprised of three or four glands which show a tendency to insinuate themselves between the internal border of the

Thirteen Additional Cases of Acute Iliac Adenitis

Case No.	Age, Sex	Symptoms	Duration	Predisposing Cause	Clinical Findings	Laboratory Data	Operation	Bacteriologic Findings	Result
6	10 M	Pain in left lower quadrant; temperature 103 F.	12 days	Pyogenic infection of skin of leg	Psoas muscle spasm on left side; mass in left iliac fossa	R.B.C. 3,560,000; hemoglobin 50%; W.B.C. 12,000; whip ova	Drainage of retroperitoneal iliac abscess	Culture not made	Discharged well in 21 days
7	2 F	Pain in abdomen; temperature 102 F.	11 days	Old cutaneous infection on right knee	Round tender mass in right iliac fossa; psoas muscle spasm	R.B.C. 3,300,000; hemoglobin 60%; W.B.C. 15,950; ascaris ova	Drainage of retroperitoneal abscess 3 cm. in diameter in iliac fossa	Staph. aureus haemolyticus	Recovery in 35 days
8	3 F	Pain in left lower quadrant of abdomen; temperature 101 F.	14 days	Not known	Hard tumor in left iliac fossa; psoas muscle spasm on left side	R.B.C. 3,200,000; hemoglobin 50%; W.B.C. 13,800; Kahn test negative	None (medical treatment)	.....	Recovery in 24 days; disappearance of mass
9	21 M	Pain in left lower quadrant of abdomen; temperature 101 F.	30 days	Cutaneous infection on left knee	Psoas muscle spasm on left side; mass in left iliac fossa	R.B.C. 2,500,000; hemoglobin 45%; W.B.C. 22,000	Incision and drainage of large iliac abscess	Staph. aureus haemolyticus	Recovery in 18 days
10	5 F	Pain in right side; temperature 102 F.; anorexia; vomiting	7 days	Not known	Mass in right lower quadrant; psoas muscle spasm	Hemoglobin 75%; hook ova in stools	Drainage of small abscess in iliac glands	Culture not made	Recovery in 14 days
11	16 M	Temperature 104 F.; abdominal pain	10 days	Not known	Psoas muscle spasm; mass in right iliac fossa	W.B.C. 31,800	Drainage of iliac abscess	Culture not made	Recovery in 29 days
12	2½ M	Pain in abdomen; temperature 101 F.; inability to extend left thigh	21 days	Trauma; fall with blow on left buttock	Tumor in left lower quadrant of abdomen; psoas muscle spasm on left side	R.B.C. 4,100,000; hemoglobin 70%; W.B.C. 9,400	Drainage of iliac abscess; 100 cc. thick pus	No growth	Uneventful recovery

13	7 M	Pain in left side; temperature 101 F.	12 days	Pain in left leg 6 months previously	Mass in left lower quadrant of abdomen; psoas muscle spasm	R.B.C. 3,860,000; hemoglobin 60%; W.B.C. 17,800; tuberculin test negative	None (medical treatment)	.....	Recovery in 14 days; disappearance of mass
14	25 M	Pain in right side; fever, malaise, anorexia	25 days	Not known	Pallor; psoas muscle spasm on right side; mass above Poupart's ligament	R.B.C. 3,200,000; hemoglobin 70%; W.B.C. 12,000	Incision over mass; drainage of thick-walled iliac abscess (appendix normal)	Culture not made	Recovery in 14 days
15	2 F	Swelling, pain and tenderness in right lower quadrant of abdomen	30 days	Impetiginous lesions on lower part of abdomen and on legs	Right thigh flexed; mass in right iliac fossa	R.B.C. 3,500,000; hemoglobin 50%; W.B.C. 18,000; tuberculin test negative	None (medical treatment)	Staph. aureus haemolyticus from cutaneous lesion	Recovery in 21 days; disappearance of mass
16	18 M	Dull pain in left lower quadrant of abdomen; inability to extend left thigh; fever	21 days	Old infected scabetic lesions of lower part of abdomen	Psoas muscle spasm on left side; mass in left iliac fossa	R.B.C. 3,480,000; hemoglobin 62%; W.B.C. 23,000; hook ova	Incision and drainage of retroperitoneal tumor, sarcoma-like, in left iliac fossa	Staph. aureus haemolyticus	Prompt recovery
17	7 M	Inability to extend right leg; pain in right lower quadrant of abdomen; fever	21 days	Pyogenic infection of right foot 3 weeks previously	Flexion deformity of right thigh; mass above inguinal ligament	R.B.C. 3,720,000; hemoglobin 60%; W.B.C. 16,200; hook ova	None (medical treatment)	.....	Recovery; disappearance of mass
18	8 M	Fever; pain in left iliac fossa; flexion of left thigh on abdomen	22 days	Pyogenic infection of skin of legs	Visible mass in left iliac region; psoas muscle spasm on left side	R.B.C. 2,290,000; hemoglobin 45%; W.B.C. 9,100; hook ova; tuberculin test negative	None (medical treatment)	.....	Recovery in 32 days; disappearance of mass

psoas muscle and the external iliac artery. The lowest gland of this chain, located behind the crural arch, is usually of fair size and is called the retrocrural gland (fig. 3). It is the gland most often involved. The majority of lymphatics which eventually terminate in the external iliac chain end in this gland. It receives efferent lymphatics from the superficial and deep inguinal glands draining the buttocks, the perineum and the lower extremity, and some deep lymphatics from the subumbilical portion of the abdominal wall (Poirir, Cuneo and Delamere [13]).

Fig 3.—A schematic representation of the pelvic lymphatic glands and the usual location of the inflammatory tumor. *E* indicates external iliac lymph glands, and *R*, the retrocrural gland.

Predominantly, iliac adenitis is a disease of childhood, especially in Latin and tropical countries, where the children of the poor wear no shoes and cutaneous infections are common. In the 92 cases mentioned in the literature, 76 patients were children or young adults. The average age in my own series was 9 years. The disease is more common in boys than in girls, the proportion being 63 boys to 29 girls in the cases reviewed and 13 boys to 5 girls in my own series. Undoubtedly the reason for this is that trauma and infection are more common

13. Poirier, P.; Cuneo, B., and Delamere, G.: The Lymphatics, Chicago, W. T. Keener Co., 1904.

in boys than in girls. The two sides of the body are equally involved, although apparently the condition is never bilateral.

Predisposing causes are (1) infection of the cutaneous areas drained by the iliac glands, (2) trauma, (3) blood-borne (metastatic) infection and (4) idiopathic factors. In the majority of cases some trifling infection of the skin of the lower part of the abdomen, the legs, the buttocks or the perineum can be found. In 11 of my cases evidences of old impetigo or of staphylococcic infection of one of these regions were present. Both Bailey [8] and Lugones [6] mentioned that the inguinal glands are usually not involved. In only 1 of this series of cases were they palpably enlarged. Explanation of this peculiar fact must lie in the developmental anatomy of the lymphatics, since inguinal adenitis is common in the adult.

A history of trauma from a fall or of a blow to the lower part of the abdomen can often be obtained (case 3). That the condition can be metastatic in origin was first noticed by Lugones,[6] who reported 3 cases in which it followed pneumonia. Lagos-García included 3 patients in whom iliac adenitis developed after typhoid fever, scarlet fever and measles, respectively. Hyman [9] included 4 cases of blood-borne infection following otitis media, boils and pneumonia.

In my series 1 case (case 5) is representative of this group. In many cases the predisposing cause remains obscure. It is possible for the local lesion to heal before the patient is aware of the developing adenitis. In this series of 18 cases, examination of 4 of the patients gave no clue to the predisposing cause.

The average duration of symptoms before medical attention was sought was seventeen days. Pain in the iliac fossa, the lower part of the abdomen or the groin is the predominant symptom. It is accompanied by fever, which is of low grade at first, the temperature gradually rising higher and higher as the suppuration advances. Most patients complain of inability to straighten the flexed thigh. Vomiting is not unusual. Pallor, malaise and anorexia are present. Physical examination discloses spasm of the psoas muscle with flexion deformity of the thigh. A mass is always present occupying the iliac fossa and can often be felt through the rectum. The leukocyte count is from 15,000 to 35,000. Mild anemia is present. Differential diagnosis is not difficult if the syndrome is known. The slow onset and long duration of symptoms, the absence of signs of peritonitis and the presence of the tumor differentiate the condition from appendical abscess. The free motion of the hip joint with the exception of extension rules out the possibility of suppurative arthritis. Roentgenograms of the spine and pelvis and negative reactions to tuberculin tests exclude the possibility of tuberculosis of the bone.

TREATMENT

Conservative treatment is recommended at first. It consists of continuous hot or cold fomentations applied locally over the mass, correction of anemia, a high caloric and high vitamin diet and general nursing care. Of the 18 patients in this series of cases, 5 were cured by this regimen. There were 10 patients who did not improve with medical treatment and who were operated on. In three instances a mistaken diagnosis of acute appendicitis was made prior to operation.

At operation an incision which offers an extraperitoneal approach is made over the mass parallel to and above the inguinal ligament. The thick-walled sarcomatoid tumor which is found is incised, and the cavity of the abscess is drained.

Cultures of material from 7 of the 12 patients operated on produced hemolytic staphylococci. It is not understood why inflammation in the retroperitoneal glands produces the hypertrophic tumor so often encountered (fig. 3). Lugones commented on the sarcoma-like appearance of the abscess. Figure 2 shows a section of the wall of the abscess in case 3, which at operation measured 3 cm. in thickness.

When incorrectly diagnosed or neglected, the abscess may point in Scarpa's triangle, at the umbilicus, into the pelvis or into the peritoneal cavity, with fatal results. Rivarola [5] reported a case in which the abscess eroded the iliac artery. With correct diagnosis the prognosis is good. No deaths occurred in the 18 cases of this report. There were 8 deaths among the 92 cases reported in the literature, a mortality rate of 6.7 per cent.

SUMMARY

Acute iliac adenitis is an uncommon clinical entity, frequently incorrectly diagnosed. It occurs usually in children and is characterized by pain in the iliac fossa, fever and spasm of the psoas muscle. A hard, tender, fixed tumor is palpable above the inguinal ligament. At operation pus is encountered deep in the mass. With adequate drainage recovery is the rule.

The scanty literature on the subject is reviewed, and 18 additional cases are reported.

NONSPECIFIC MESENTERIC ADENITIS

A REPORT OF ONE HUNDRED AND FORTY CASES

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There is an ever present fear in the minds of surgeons of failing to recognize acute appendicitis. High mortality and prolonged morbidity are still prevalent as a result of delayed operative intervention. On the other hand, the frequently expressed opinion that it is better to operate in cases in which the diagnosis is incorrect than to overlook a bad appendix has carried physicians far afield. As a result of this state of mind, little thought is given to many diseases presenting symptoms that closely resemble the syndrome of acute appendicitis. The pathologic report on a removed appendix is often no criterion of the actual condition of the abdomen. Such changes as congestion or cellular infiltration are frequently only a comparatively small part of a pathologic process originating elsewhere in the abdomen.

It is of comparatively recent date that mesenteric adenitis has received some attention in medical literature; many of the papers are reports of a few cases in which the diagnosis was not made before operation. Most authors admit their inability to recognize this disease and therefore operate on all patients exhibiting symptoms of appendicitis even when mesenteric adenitis is suspected. Wilensky and Hahn spoke of acute mesenteric adenitis as a distinct disease entity. Their report was outstanding in many respects, but they failed to mention signs or symptoms that would enable the diagnostician to differentiate the disease from acute appendicitis. Pribram, in a lengthy paper, concluded that mesenteric adenitis should be studied more carefully, and he stressed the futility of operation for that condition. In his small series of cases the diagnosis was not made prior to the operation. MacFadden pointed out one possible distinguishing sign, but in my experience it is not pathognomonic and cannot be relied on for a correct diagnosis. Speese gathered a comparatively large number of cases from the literature. He agreed with Wilensky and Hahn that mesenteric adenitis is a disease entity, but he stated that it is impossible to make a diagnosis

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All experiments were performed at the Morrisania City Hospital.

From the surgical departments of the Morrisania City Hospital and the Bronx Hospital.

of the condition. Some authors have stated that the cause is acute appendicitis and that removal of the appendix is necessary.

As will be shown later, the diagnosis of mesenteric adenitis is not an elusive mystery, but is rather simple. It is, however, of the utmost importance to bear in mind the essentials of the anatomy and physiology of the mesentery and of the glands situated between its leaves.

In this series were 140 cases which came to my personal attention. Of the first 100, in every alternate case exploration was made to corroborate the diagnosis.

The mesentery of the small intestine begins at the left side of the second lumbar vertebra near the duodenojejunal attachment and runs diagonally downward and to the right, ending near the right sacroiliac articulation. It is about 15 cm. long at its root, but after spreading out into the shape of a fan it attains a length of 5 meters at its intestinal attachment and is therefore freely movable throughout, except at the ends. The mesentery of the terminal portion of the ileum differs in important details from the rest. A clear understanding of the anatomic arrangement of this area will make the diagnosis simpler. The last 6 cm. of the mesentery of the ileum is free from glands. Its fibers converge from left to right, and no vessels traverse this space. It is often called the avascular space of Treves. On the posterior surface of this fold is a space called the ileocecal fossa; an occasional small blood vessel is seen traversing it from left to right (fig. 1).

The lymphatic drainage of the intestines is accomplished by means of two sets of vessels. One set originates in the mucosa and the submucosa; the other takes its origin in the muscularis and the subserosa. The former is in close association with Meisner's plexus, and the latter with Auerbach's plexus. The submucosal plexuses receive the efferent lymphatics from the intestinal villi draining the lumen of the intestines; those coming from the muscularis and subserosa are fewer and drain the intestinal wall. The efferent lymphatics of the mucosa run directly into the mesenteric leaves, emerging at their attachment to the intestines; those coming from the intestinal wall often run some little distance before joining the more voluminous trunks, with which they enter the mesentery. These combined channels form the collective trunks known as Oselli's chylifers (collectives of the jejunum and ileum). Some authors have described three distinct sets of glands in the mesentery grouped along the avascular arcades. Rouviere, in his extensive studies, failed to find the lymphatic glands in distinct groups. My experiments bear out his observations.

The following experiments were made on living subjects in the course of laparotomies on both animals and human beings. With a 28 gage needle (this size being used to avoid too much pressure), a 1

per cent solution of indigo carmine was injected into the subserosa of the ileum both longitudinally and transversely. The dye ran along the intestinal wall for about 2 cm. and then, turning abruptly downward, entered the mesenteric leaves. The lymphatic channels became clearly outlined in irregular streaks; some of the dye entered glands a little distance from the intestines; the rest proceeded downward. The dye often circumscribed one or more glands, continuing downward toward the spinal column and finally coloring the glands at the root. These were found to be somewhat oval and larger than those at the free border. The drainage from the lowermost part of the ileum (corresponding

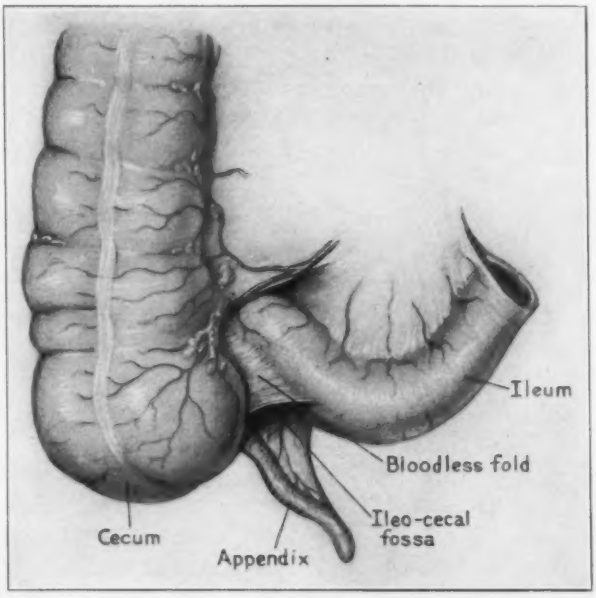

Fig. 1.—The avascular space of Treves, where no glands are found. This area drains into the same chain of lymphatics as do the appendix and the cecum. (After Treves.)

to the avascular space of Treves) is from left to right. The lymphatics run to the satellite nodes of the ileocecal artery. These may join the rare ganglionic nodules close to the iliac branch of the artery or to the terminal branch of the superior mesenteric artery.

The lymphatics of the appendix are not independent of those of the cecum and will be considered together. The cecum has two sets of lymphatics, one set emerging from the anterior wall and another set emerging from the posterior surfaces. Both run toward the ileocecal chain directly or through the intermediary of the anterior and post-

cecal glands. A number of lymphatic glands are found in the ileocecal angle that drain the appendix, the cecum and the lowermost small segment of the ileum. These drain along the mesenteric artery, running diagonally upward and emptying into the chain near the third portion of the duodenum. The glands of the rest of the large intestines are similar to those of the jejunum and the ileum in their arrangement, but are not so numerous (fig. 2).

The physiology of the lymphatics of the small intestines is well known. The retrograde flow described by Braithwaite has not been corroborated. His experiments were carried out on cadavers, and the

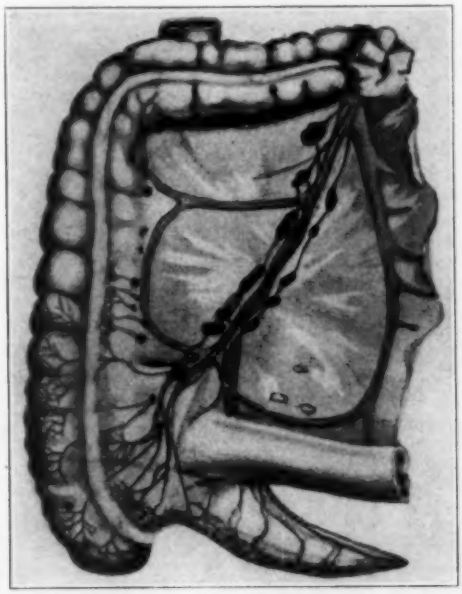

Fig. 2.—Lymphatics of the cecum and appendix. The collected lymph takes the direction of the superior mesenteric artery and empties into the area of the third portion of the duodenum. (Gray, Henry: Anatomy of the Human Body, edited by W. H. Lewis, Philadelphia, Lea & Febiger, 1930.)

results cannot be substantiated by observations on living subjects. I failed to duplicate his experiments on living animals. The intestinal glands empty into the thoracic duct and thence into the general circulation. The reverse process is physiologically not possible.

The pain of mesenteric adenitis is not easily explained, though there is some knowledge of the mesenteric response to external stimuli. While it is true that the intestines are insensitive to such stimuli as cutting, pinching and burning, the ganglionic plexuses of Meisner and Auerbach may be responsive to some forms of stimuli that cannot be

produced artificially. In the mesenteric leaves are found the pacinian corpuscles, which are undoubtedly sensory end organs. The mesenteric leaves are sensitive to pulling in either direction, as can be verified by tying a ligature or by cutting in the course of a laparotomy under local anesthesia. Inflammation and hyperplasia of the glands, causing pressure on the sensory organs, or their direct invasion by toxins is a possible explanation.

The cause of mesenteric adenitis, as was suggested by Wilensky and Hahn, Pribram and others, is absorption of toxins from the intestinal tract. These toxins may be of bacterial origin or may be the products of digestion. The statement that mesenteric adenitis is preceded by an infection of the upper respiratory tract is not borne out by careful histories and close observation. It is also contrary to the normal physiology of the animal body. The fact that mesenteric adenitis is always accompanied or immediately preceded by inflammation of the intestines, as observed at operation, is further evidence that this form of adenitis is a direct result of pathologic conditions in the intestines. There is a small group of cases of very acute involvement in which infection of the upper respiratory tract occurs simultaneously with mesenteric adenitis. In these cases it is perhaps a general toxemia that brings the toxins to the intestines via the blood stream, causing inflammation with consequent glandular hypertrophy. Another possible explanation is that bacteria may pass the stomach, whose normal function is disturbed and its bactericidal action diminished. The organisms entering the alkaline medium of the small intestines proliferate rapidly. In fact, in a great majority of cases, particularly in those of the subacute form, there is no history of a preceding infection of the upper respiratory passages. In only 8 per cent of my series was there such a history.

One often observes that interns rule out mesenteric adenitis as a possibility if no such history of infection is elicited. If the pain is in the right side of the abdomen it is usually diagnosed as subacute or chronic appendicitis. Another observation is that mesenteric adenitis occurs mostly in the small intestines, and in the majority of cases in the lower 4 or 5 feet (124 to 152 cm.) of the ileum (except in the avascular space of Treves). Here the intestinal products of digestion are toxic and absorption is great. The statement, frequently heard, that this form of adenitis is due to an inflamed appendix is utterly incorrect and contrary to anatomic arrangements. As pointed out by Wilensky and Hahn, in acute appendicitis the mesenteric glands of the ileum are not involved. In this connection it may be pointed out that postoperative abdominal pain, so often felt by young adults, occurs mostly after so-called subacute or interval appendectomies. It is usually explained by the timeworn aphorism of postoperative adhesions or neurosis. Pribram's statement that such pain is in many cases due to

continued inflammation or to repeated attacks of mesenteric adenitis is probably correct. Felsen suggested that the cause factor of mesenteric adenitis may be a form of bacillary dysentery. In this series no thorough study was made, but of 30 studied cases in only 3 was there positive agglutination. The general impression that diarrhea accompanies enteritis is erroneous, as was pointed out by Felsen in his studies of bacillary dysentery.

When the abdomen is explored a few days after the onset of the disease, the acute inflammation of the intestines may have subsided. There remains, however, some thickening of the wall, and the color is often seen to be a light pink. Perhaps in some cases the toxins enter the lymphatic channel directly from the mucosa without affecting the wall of the intestines.

The frequency of mesenteric adenitis cannot be estimated with any approach to accuracy. For 18 of 100 consecutive children and adolescent patients admitted to my service in the wards with a diagnosis of acute or subacute appendicitis, a diagnosis of mesenteric adenitis was made after examination and proved correct at operation. Still, quoted by MacFadden, found that 59 per cent of children on whom autopsy was performed had enlarged mesenteric glands. This disease is prevalent in children and adolescents and is rare in adults. I have observed only 1 adult patient, a man 30 years of age. I failed to make a diagnosis, his being one of the early cases. The youngest patient in whom the disease was recognized was 3 years old. The average age of the patients in this series was 12.1 years; 58 per cent were girls and 42 per cent boys.

That the diagnosis of mesenteric adenitis is not difficult may be gathered from the fact that my house surgeons have learned to recognize this condition with remarkable frequency. In this series we had 2 cases in which the condition was not diagnosed correctly, the case of the 30 year old man, just mentioned, and the case of a child acutely ill, with a temperature of 105 F., in which we made the diagnosis of toxemia due to streptococcic infection of the throat, with inflammation of the intestines and the mesenteric glands. A note on the chart mentioned the possibility of appendicitis but added that the patient was too ill to be operated on. After thirty hours, when the temperature was much lower an exploratory laparotomy was performed and acute appendicitis was found. The whole intestinal tract was highly inflamed, the intestinal wall much thickened and the glands in the mesentery enlarged. The patient recovered.

Nonspecific mesenteric adenitis can be roughly separated into three types. The first is the least common and in this series only 8 cases occurred, all the patients being between 6 and 12 years of age. A sudden onset within twenty-four hours, with a temperature ranging

between 105 and 106 F. and marked toxemia, were common to all. The blood picture in such cases is apt to be alarming. A white cell count amounting to 20,000 or more, with a differential count showing from 80 to 90 per cent polymorphonuclears, is common in the first twenty-four or forty-eight hours. The proportion of band forms may be as high as 30 per cent. All these symptoms occur within the first six hours of the onset. Examination of the patient reveals the following picture: a flushed face, rapid pulse and marked congestion of the throat. If the patient has been ill more than twenty-four hours a membrane covering the tonsils may be seen. The abdomen is somewhat distended and tender throughout, especially in the right lower quadrant. When operated on the whole intestinal tract, particularly the small intestines, is thickened and extremely red. In the mesentery the glands are found to be deep pink. Those near the intestinal attachment are small, round and of deeper color, while those near the root are larger and somewhat oval. The appendix is congested, as is the cecum.

With the second type, which is the most common and is often mistaken for appendicitis, there usually is the following history: The patient is a child or a young adolescent and complains of intermittent abdominal pain which has lasted for one day or longer. The pain is at first rather severe but becomes somewhat less so on the second day. Nausea is present, but vomiting occurs only in about 40 per cent of the cases. When vomiting is present it usually occurs four hours or more after the onset. The pain may subside for a few hours but recurs at frequent intervals. When questioned as to the location of the pain the patient will point to the right lower quadrant of the abdomen. There is neither constipation nor diarrhea. In the first twenty-four hours the temperature ranges around 102 or 103 F., but it recedes within twelve to twenty-four hours to approximately 100 or 101 F. The blood count during the first day is about as follows: the number of erythrocytes is normal; the number of white cells is high, often 18,000, with a differential count showing 80 per cent or more polymorphonuclear leukocytes. The shift to the left is between 12 and 20 per cent. The following day the white blood cell count recedes to about 10,000 and the shift to the left recedes in a similar proportion. Results of urinalysis are negative.

In a recumbent position the patient appears comfortable. Abdominal reflexes are normal, since the parietal peritoneum is not involved. Gentle percussion may elicit slight tenderness about 4 cm. to the right and a little below the umbilicus. This is the first differential point, as in appendicitis gentle percussion will always elicit pain over the base of the inflamed appendix. On palpation, no rigidity can be discovered, though at times there is a mild resistance over the right side which can be easily overcome when the patient's attention is diverted. There is always a moderate degree of rebound tenderness throughout the lower

part of the abdomen, but the sudden removal of the palpating hand from the left lower quadrant does not cause rebound tenderness on the right side. Tenderness is found over a small area to the right of

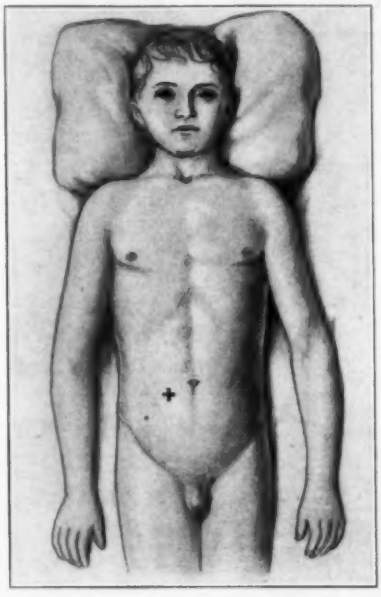

Fig. 3.—The tender point in mesenteric adenitis is at a higher level than in appendicitis and is internal to McBurney's area.

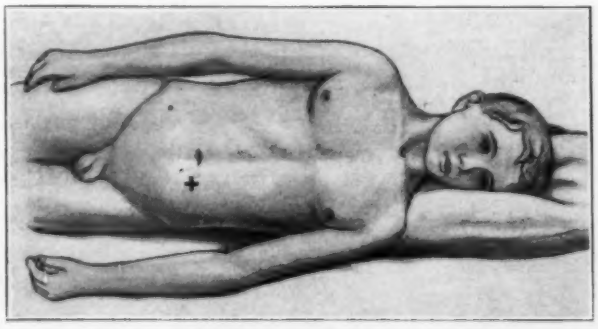

Fig. 4.—When the patient is turned to and allowed to rest on the left side, the tender area is shifted to the left and is absent on the right, as indicated by the cross.

the umbilicus, but much higher than McBurney's point. The tender area may extend even above the umbilicus on the right side. The left side at this time is free from tenderness. The patient is then turned on the left side and allowed to remain in this position for thirty seconds

or more. Palpation in this position finds the tender area previously noted on the right side now shifted to the left of the umbilicus and absent on the right side (figs. 3 and 4). The patient is turned on the right side and allowed to rest for a short period, and palpation then reveals absence of tenderness on the left side and more marked tenderness on the right. In this position the tenderness in the area in question is more extensive than when the patient was resting on his back. This shifting tenderness is easily explained if one remembers the anatomic outline of the mesentery. When the patient is turned on either side the mesentery and small intestines will gravitate to the extreme dependent part of the abdomen. The cecum and appendix have little mobility and cannot be shifted to the left with a change of

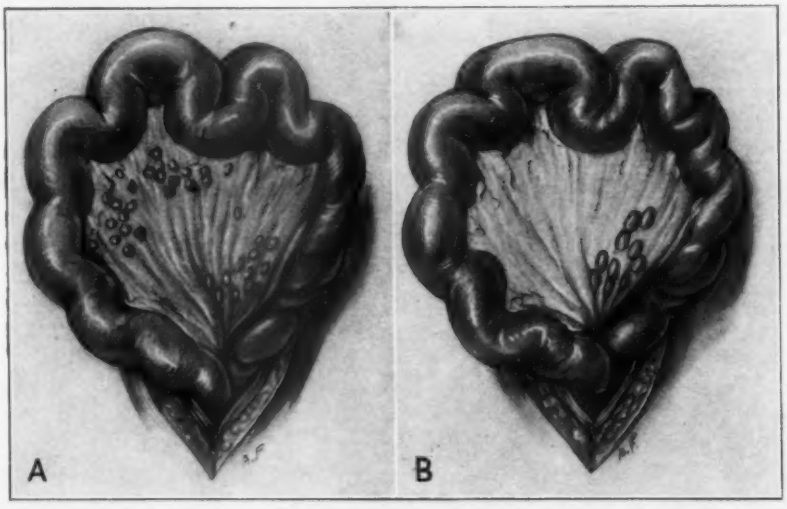

Fig. 5.—*A*, early stages of hyperplasia. The glands are found near the intestinal attachment of the mesentery and at the root. *B*, appearance three or more days after the onset. The glands are absent near the intestinal attachment of the mesentery but persist near the root.

the position of the body. This one sign, when present, has always differentiated mesenteric adenitis from acute appendicitis. The findings at operation in this type of mesenteric adenitis depend on the length of time which has elapsed since the onset. If exploration is made during the first twenty-four hours, the findings are somewhat as follows: The small intestine shows inflammation, which is most marked in the last few feet of the ileum. This inflammation may be segmental, that is, one may find areas of inflammation with intervening parts of normal appearance. The glands are usually small and pinkish near the mesenteric attachment, while lower down they are larger and oval (fig. 5 *A*). If operation takes place three or more days after the

onset, the small intestine may be found normal in appearance, but thickened, and the mesentery near the intestines free from glandular enlargements. Lower, nearing the spine, the glands are present in small groups and are lighter in color (fig. 5 *B*). They sometimes attain the size of a small walnut. In cases of recurrent involvement the glands are found near the spinal attachment and are never so large. These are much harder than in the early stages. This condition may persist for a long time. In some cases when operation is delayed one or more weeks the ileum is found normal in appearance. It is perhaps possible

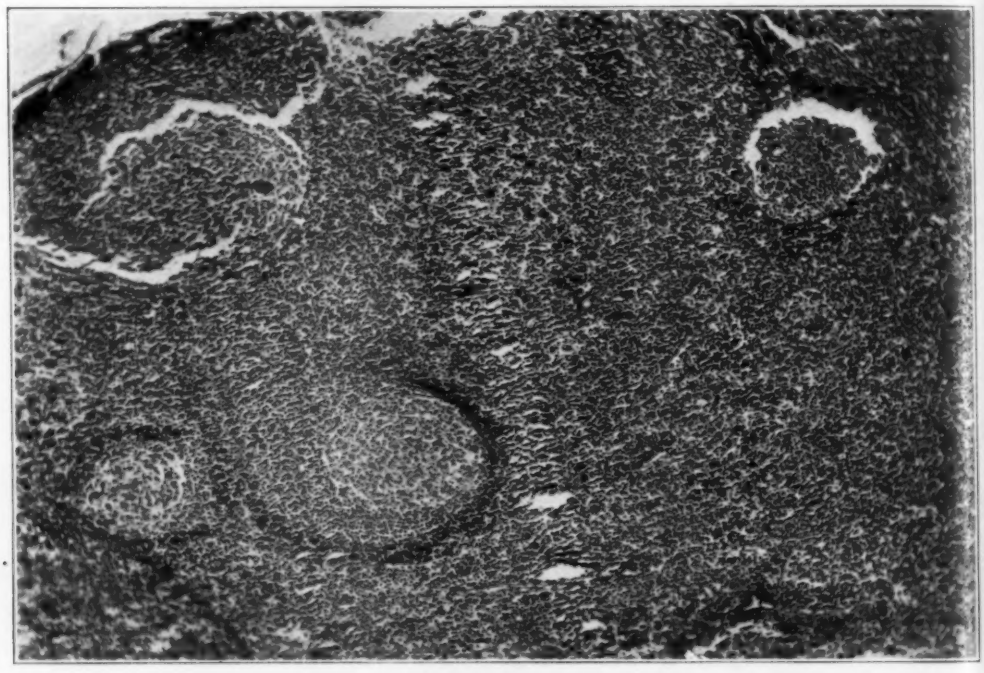

Fig. 6.—Various stages of mesenteric hyperplasia in nonpyogenic adenitis of the mesentery.

that absorption of the toxic agent takes place directly into the mesentery lymphatics from the mucosa without involving the muscularis and the serosa.

The third type gives the same history as the second, but with this type examination of the abdomen discloses that whereas the tenderness can be shifted from right to left with change of position there persists a tenderness over the cecum. This type cannot always be differentiated from a pathologic process which involves the appendix. The findings at operation are somewhat as follows: The small intestine, particularly the lower ileum, is moderately inflamed, the cecum more so.

In the mesentery of the ileum the glands are enlarged. In the ileocecal angle is found a conglomeration of four or five glands markedly infiltrated, and the appendix is congested and much thickened. In this connection it is interesting to note that one often hears cases of the condition just described reported as proving that mesenteric adenitis is caused by an acute condition of the appendix. The explanation of this pathologic process lies, in my opinion, in the occurrence of an intestinal infection, due either to putrefaction or to bacterial invasion, which causes an inflammation of the ileum, the cecum and part of the ascending

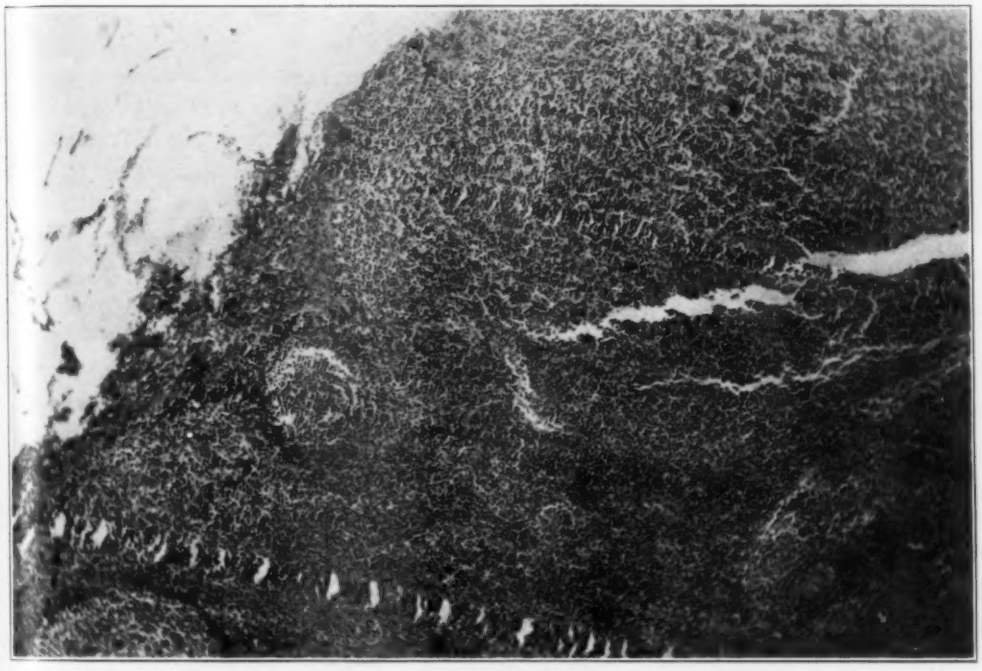

Fig. 7.—Various stages of mesenteric hyperplasia in nonpyogenic adenitis of the mesentery.

colon. The involvement of the appendix in these cases is only part of the whole process. A contributing factor is possibly interference with the normal circulation of blood in the appendix by the enlargement of the glands in the ileocecal angle. The patients must be watched carefully. If rigidity occurs and the polymorphonuclear leukocyte count remains high, the abdomen must be explored. This form of ileitis should not be confused with the terminal ileitis described by Ginzberg and Crohn and others. The pathologic process and the symptoms of terminal ileitis are entirely different, and the course is progressive. In this series I have not encountered the pyogenic form of adenitis.

The pathologic report of the appendixes and glands removed during laparotomies in these cases is of special interest. From all patients laparotomized the appendix was removed, and in 20 cases one or more glands were removed for study. Felsen studied some of these appendixes by injecting the lumen with barium sulfate and correlating his findings with the histologic evidences, using a suitable number of normal controls. He found the mucosa intact, and sections failed to show actual pathologic conditions. Congestion was present in a small number of the appendixes. All glands removed proved to be sterile on culture; sections showed cellular infiltration, as can be seen in figs. 5 *A*, 6 and 7.

For the patients on whom operation had not been performed and who were under observation in the hospital for five days or more, the following routine was adopted: All solid food was interdicted for at least four days. During this period fruit juices were given freely and boiled milk in small quantities. Liquid petrolatum was given to overcome possible constipation, but all irritating cathartics were avoided.

The patients operated on had an uneventful convalescence.

As most of the patients were in the wards a thorough follow-up was impossible. Only 50 patients (25 of whom had been operated on) were observed from one to two years after either observation or operation. Both sets of patients had repeated mild attacks of abdominal pain. An interesting observation was that private patients not institutionalized continued to have severer attacks of pain than those kept under observation in the hospitals, though the latter came from much poorer surroundings.

CONCLUSIONS

1. Mesenteric adenitis is much more common than is generally recognized.

2. A diagnosis is possible in a majority of cases.

3. Mesenteric adenitis is not necessarily an accompaniment of an infection of the upper respiratory tract.

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DISTRIBUTION AND EXCRETION OF WATER AND CHLORIDES AFTER MASSIVE SALINE INFUSIONS

AN EXPERIMENTAL STUDY

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Massive intravenous infusion has become an accepted therapeutic measure of wide application among practitioners of medicine and surgery, and present trends in medical practice seem to indicate even more extensive use of the method in the future. Nevertheless, comparatively little is definitely known about the physiologic responses of the body to the direct artificial addition of solutions of inorganic substances to the circulation. This is because the procedure has developed primarily at the bedside rather than in the experimental laboratory. Moreover, as ordinarily practiced, it has proved almost completely devoid of danger to life.

Because of the simplicity of the common vehicles of infusion—watery solutions of sodium chloride and dextrose usually—the consideration of intermediate metabolism has not seemed to most practitioners a serious issue, and the attention of experimentalists has turned, rather, to such matters as the causation and prophylaxis of the postinfusion reaction. It is true that attention has been paid to the assimilation and elimination of dextrose when used in infusions, and some consideration has been given to the factor of hypertonicity. By and large, however, the fundamental proposition that parenterally administered fluids are the physiologic equivalents of the same fluids administered by mouth has never been subjected to thorough experimental investigation.

The experiments to be reported in this communication were originally designed to determine the maximum rate of infusion compatible with survival and the lethal dose of essentially isotonic solutions of sodium chloride. It was moreover proposed to discover the cause of death after such lethal infusions and to trace the intermediate assimilation, trans-

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location and excretion of both the sodium chloride and the water when given in just sublethal amounts. As so frequently happens in experimental work, the original aims have not been entirely fulfilled, but important facts have, we believe, been collected. This investigation is, of course, but part of a much larger one, involving parenteral administration of solutions in other concentrations, of other substances and by other methods than intravenous injection. Until the general problem has been studied in all of these aspects, it cannot be assumed that the results of this study are applicable to all types of parenteral administration.

TECHNIC

In the experiments now to be reported, cats exclusively were used as experimental animals. No particular selection of animals was made with respect either to size or to physical condition. They were stock animals, which for varying periods had been fed ordinary laboratory rations, including as much water as they would drink.

Intraperitoneal injection of solution of dial and ethyl carbamate (urethane) [1] (0.9 grains [0.054 Gm.] of diallylmalonylurea per kilogram of body weight) was practiced routinely for anesthesia. In a few instances, in which the initial level of anesthesia produced by this agent was not deemed sufficiently deep, a little ether was temporarily given by inhalation to facilitate the primary operative procedures.

The intravenous infusions were given from a standard graduated arsphenamine buret holding 300 cc., which was connected by means of a short piece of rubber tubing to a glass cannula. This was inserted into the jugular vein (usually on the right) except in some cases in which the femoral vein was selected for special reasons. The arsphenamine tube was attached to a buret stand at such a level that the height of the column of fluid above the cannula varied from about 25 inches (63 cm.), when the tube was full, to about 16 inches (40 cm.), when the level of fluid had dropped to the last graduation.

In such a gravity system the speed of injection depends not only on the head of hydrostatic pressure but on the available caliber of the injectional system at its narrowest point, which ordinarily is the point of junction between the venous cannula and the vein. This narrowest part of the system is subject to variations in caliber from moment to moment because of such factors as twisting or change in angulation of the cannula with respect to the vein. These variations cannot be altogether avoided because living animals cannot be absolutely immobilized. Because we were anxious to maintain strictly constant rates of injection, we originally used the principle of the Mariotte flask in order to stabilize the hydrostatic pressure. We soon found, however, that the variability which resulted from fluctuations in the pressure was of little importance compared with that due to changes in caliber. Therefore, we ultimately fell back on the simple expedient of keeping the system adjusted practically to the full caliber of the vein. Minor variations were compensated by slight manipulation of a screw clamp and all our adjustments gaged by constant checking of the rate of fall of the meniscus in the buret.

We sought to avoid as much as possible the debatable point as to how strong a solution of sodium chloride constitutes an exactly isotonic or physiologic solution

1. Obtained through the courtesy of the Ciba Company.

for the cat. Therefore, we have arbitrarily selected the strength of 1 per cent as being sufficiently close to the proper value for practical purposes. This figure is nevertheless not so exactly the proper value as to make it appear that we consider isotonicity actually critical.

In most of the acute experiments tracheal cannulation was performed, and blood pressure and respiration were continuously recorded on a long paper kymograph. The blood pressure was taken by direct cannulation of the common carotid artery and the respiration recorded from the tracheal cannula through a rubber tube connecting with a sensitive tambour.

PRELIMINARY EXPERIMENTS TO DETERMINE THE "LETHAL DOSE" OF SOLUTIONS OF SODIUM CHLORIDE

Our recorded tabulation (table 1) includes results from 10 cats. A considerably larger number of animals was actually used, omissions in

TABLE 1.—*Rates of Injection and Total Amounts of Sodium Chloride and Water in Lethal Doses of Saline Solutions Administered Intravenously* *

Cat Number	Strength of Sodium Chloride Solution, %	Weight of Animal in Kg.	Rate of Injection in Cc. per Kg. of Body Weight per Min.	Total Volume in Cc. per Kg. of Body Weight	Total Sodium Chloride in Cc. per Kg. of Body Weight per Min.
2A	1	1.53	7.71	503	5.03
9A	1	2.95	6.68	517	5.17
10A	1	2.77	4.04	639	6.39
11A	1	2.88	4.44	446	4.46
3A	2	2.50	5.68	320	6.41
4A	2	2.78	4.53	241	4.82
7A	2	2.90	3.93	196	3.93
8A	2	3.45	3.24	362	7.24
6A	5	2.40	1.66	170	8.50
5A	10	1.76	4.23	55	5.51

* The injections were continued at a constant rate until death occurred.

the final record being made in order to avoid unnecessary compounding of evidence. Four cats received a 1 per cent solution of sodium chloride, 4 others a 2 per cent solution and the 2 remaining a 5 per cent and a 10 per cent solution, respectively.

The death of the animals in all cases was obviously due to the injection of sodium chloride in water, and the fatal dose is a matter of record. It is not, however, strictly accurate to speak of this as the lethal dose in the same sense as that in which the term is applied to intrinsically toxic substances. Both water and sodium chloride are, of course, normal constituents of the blood stream, and they become toxic only fortuitously, when their relative concentrations are grossly disturbed. The data for the first and the last animal of the preceding table clearly exemplify this statement, since both received approximately the same amount of sodium chloride, yet the first tolerated approximately nine times as much water as the last before death occurred, the solution which the last received being ten times as concentrated. Intermediately placed in the

series are 2 animals, 9A and 10A, which received considerably greater amounts of water than either of the other 2 animals. From these observations it may be concluded that water is not the lethal agent.

Furthermore, sodium chloride does not appear to be the lethal agent either, for there are animals intermediate in the series, 3A, 6A, 8A and 10A, which tolerated before death occurred considerably greater amounts of sodium chloride than did either the first or the last animal.

The logical conclusion is, of course, that neither of these agents is toxic in itself and that separately, therefore, they cannot be said to have any assignable lethal dose. In combination, however, they do appear to produce death after certain amounts have been given. The necessary amount depends on the concentration of the salt in the solution and undoubtedly also on the rate of its administration. The lethal dose of any given solution injected at any given constant speed is undoubtedly constant for any given concentration.

That hypertonicity (or hypotonicity) is a factor of great importance in determining the lethal dose is strongly indicated by the reactions of the animals in this short series. They appeared definitely less tolerant of a 2 per cent solution than of a 1 per cent solution. In still higher ranges of concentration (5 per cent and 10 per cent) it appears that much smaller amounts are fatal. At such concentrations rates of injection must be greatly reduced or death ensues rapidly.

The only conclusion for our present purposes which we wish to draw from this short series of animals is that cats tolerate the intravenous injection of tremendously large amounts of solution of sodium chloride at a rapid rate, provided the solution is not more concentrated than 2 per cent. The lethal amount is of the order of 500 cc. per kilogram of body weight for 1 per cent solutions and 275 cc. for 2 per cent solutions when the injection is made at the speed of approximately 5 cc. per kilogram of body weight per minute. Translated into terms of a human being weighing 70 Kg., or 154 pounds, this would be a total of 35 liters of 1 per cent solution, given at the rate of 350 cc. per minute. This is, of course, a much more massive volume and a much more rapid rate of injection than is actually used in clinical practice. It is therefore questionable whether death has ever resulted in a human being merely from the injection of the weaker solutions of sodium chloride, as such.

Milbert [2] said that he felt he had grossly exceeded what are customarily considered the limits of safety when he used in a series of clinical cases a rate of injection between 0.83 cc. and 2.5 cc. per kilogram of body weight per minute, though the total amount of solution was

2. Milbert, A. H.: Infusion Reactions with Special Reference to "Speed Shock," Am. J. Surg. **26**:479-485, 1934.

in many cases less than 1,000 cc. To be sure, he used some solutions which were hypertonic (2 per cent and 5 per cent solutions of sodium chloride and 10 per cent solutions of dextrose). The fact that Milbert's patients suffered no ill effects attributable to the rate of infusion corroborates the belief that such quantities and rates are conservative rather than radical.

It is not a new or recent observation that experimental animals tolerate the intravenous infusion of huge quantities of saline solution. Dastre and Loye [3] published in 1888 a convincing communication describing the introduction of suitable fluids (0.7 per cent solutions of sodium chloride) into the circulation of rabbits and dogs. They injected amounts totaling as much as three quarters of the body weight within the relatively short period of three to seven hours. These injections produced no unfavorable effects, either immediate or remote, in two months of observation. We can corroborate this result unreservedly for postinfusion periods of several days to two weeks, though we have seen no occasion to prolong the observation of recovery beyond such limits.

A. Effect of Massive Infusions on Blood Pressure.—The capacity of the vascular system is constantly shifting by virtue both of (1) its vasomotor reactions, which tend to adapt its capacity to the cubic measure of its contents, and of (2) the permeability of its immense capillary system, which seems to change both locally and generally in accordance with a number of different physical and chemical factors. It is therefore impossible by any means at present available to determine how long any artificially injected soluble substance remains in the circulation. This is particularly true of solutions of sodium chloride because of their extreme diffusibility.

The best that can be done is to attack the problem indirectly. A long series of tracings of blood pressure, taken during the large, rapidly administered infusions which we have employed, serves to show conclusively that the blood pressure is neither constantly nor greatly affected. A representative tracing, somewhat condensed, is reproduced in figure 1.

In general, if the blood pressure is somewhat low at the time the infusion is started a temporary rise is produced, which tends to be well sustained. If, on the contrary, the blood pressure is moderately high at the beginning of the infusion, it customarily decreases slightly within a short time and thereafter remains at about the same level throughout the infusion. In general, the blood pressure is maintained at a satisfactory level throughout a fatally large infusion and falls abruptly just

3. Dastre, A., and Loye, P.: Le lavage du sang, Arch. de physiol. norm. et path. **2**:93-114, 1888.

as death is occurring. A slight progressive decrease in blood pressure throughout the entire course of the infusion is the rule.

Every indication points to a marked increase in the volume of circulating blood during such infusions. Hematocrit estimations show increasing preponderance of fluid over cells and increase in the water content of the blood is revealed by drying successive samples to constant weight. Therefore a fairly stationary blood pressure at a relatively high level can mean only that great compensatory vasodilatation occurs.

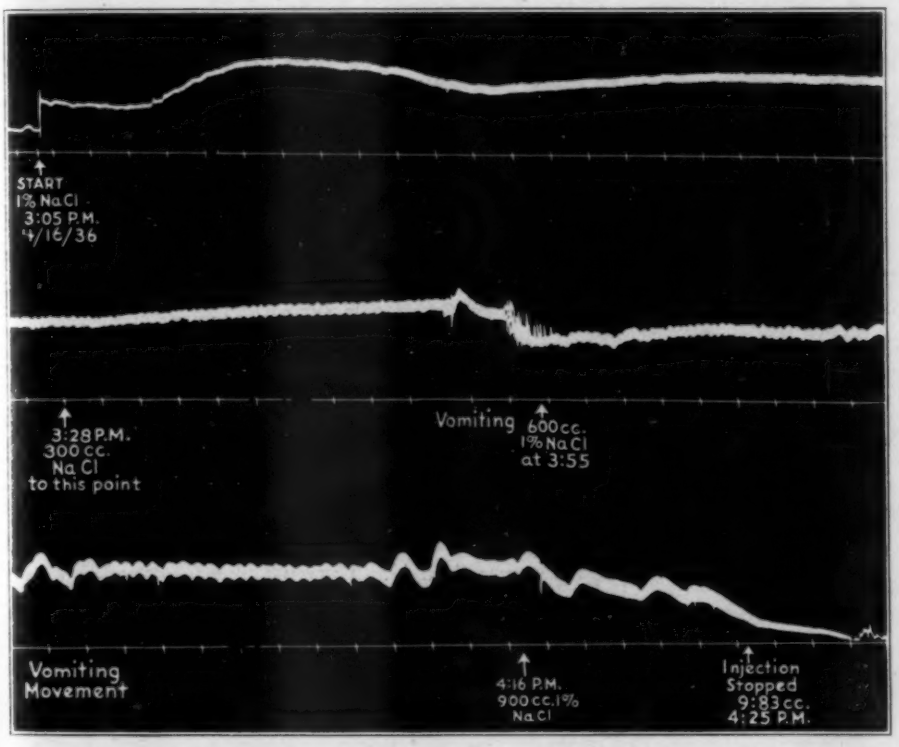


Fig. 1.—A characteristic tracing of blood pressure; the kymogram has been cut in three sections, which are reproduced one under the other. Note the relatively constant level sustained throughout a continuous massive infusion of 1 per cent solution of sodium chloride (983 cc. in a cat weighing 1.76 Kg.).

B. Gross Pathologic Observations.—It was hoped that examination of the various tissues and organs of the cats at autopsy would give some definite clue as to the cause of death after massive infusions. This hope was by no means completely fulfilled, for although definite changes were evident they were diffuse, and it was therefore impossible to attribute the fatality to the failure of any particular organ or system.

For the animals which died from the effects of massive doses of 1 per cent saline solution typical postmortem observations were as follows:

General Appearance.—The animal's abdomen was considerably distended; watery yellow fecal material was streaming from the rectum; urine was trickling from the urethra, and watery mucoid material was dripping from mouth and nose.

Peritoneal Cavity.—The peritoneal cavity contained some slightly blood-stained free watery fluid, the amount of which was estimated at 100 cc. (The staining with blood was probably the result of the action of dial on the peritoneum.)

Gastrointestinal Tract.—The walls of the stomach were thick, white and edematous; the cavity of the organ contained a small amount of bile-stained watery material. Both large and small intestine were thick, white and edematous; both were moderately filled with watery fecal material. The amount of material which the gastrointestinal tract contained was much less than one would suppose from the appearance of its various parts before incision. Most of the apparent distention which was seen from the peritoneal surface was actually due to the great thickness of the walls of the intestine.

Pancreas.—The pancreas was completely water logged, pale pink and friable; the structural elements of the organ were widely separated by gelatinous material. Altogether, the organ was several times its normal size. The cut surface did not exude much fluid unless squeezed or minced with a knife.

Kidney.—The organ showed no particular enlargement. The capsule stripped easily. Thus exposed, the organ was pale and tense and bled freely from its cut surface.

Adrenal Glands.—Except for some possible enlargement, the adrenal glands were apparently normal.

Urinary Bladder.—The bladder appeared distended, but when it was opened the appearance seemed to be due not so much to the quantity of urine it contained as to the thick, edematous condition of its walls. Such urine as it did contain was clear and colorless.

Gallbladder.—The gallbladder was dark bluish green and was distended with bile.

Liver.—Aside from some questionable enlargement, the liver presented a normal appearance.

Retroperitoneal Space and Space Between the Leaves of the Mesentery.—These spaces presented a remarkable appearance, as if widely distended with fluid. Cutting into the tissues, however, revealed that the appearance was due to a gelatinous edema rather than to an accumulation of free watery material. Little fluid escaped spontaneously from the cut surface.

Thoracic Cavity.—There was judged to be a slight excess of free fluid in the thoracic cavity. It was clear and watery in appearance, and its amount was estimated at 10 cc.

Lungs.—The dependent portions of both lungs were dark red and mottled; the upper lobes were pink and crepitant. The entire organ showed a frothy edema when cut and squeezed, and the lower lobes exuded a clear, serous fluid from the cut surface, which dripped when this part of the organ was compressed. Squeezing the entire organ caused frothy exudate to appear at the opening in the neck formed by tracheotomy.

Salivary Glands.—The salivary glands were swollen, pale and edematous.

Other Tissues and Organs.—All other organs, including the thyroid gland, the brain and the heart, appeared normal. In general, the tissues were diffusely pale, swollen and edematous, but they did not pit on pressure.

The observations on the animals which died from the infusion of 2 per cent solution of sodium chloride were superficially similar, but different in certain details. The elements of similarity included the abnormal amounts of free fluid in the abdominal cavity, the characteristic and striking gelatinous edema between the leaves of the mesentery and in the retroperitoneal space, the gelatinous edema of the pancreas and the watery edema of the stomach, intestine, and salivary glands. Among the most characteristic respects in which the latter group of animals differed from the former were the following:

1. Although the intestine was white and edematous, the small intestine was tightly contracted and beaded, the large intestine only being dilated.

2. The kidneys, though somewhat swollen, instead of being pale were dark and brownish, and the cut surface showed hemorrhagic areas about the pyramids.

3. The heart showed extreme contraction, with complete emptying of all its chambers.

4. The lungs showed much less edema, but scattered areas of punctate hemorrhage were noted.

Comment.—All in all, comparison of the postmortem observations on the animals which died from the effects of the 1 per cent solution and those on the animals which died from the effects of the 2 per cent solution tends to support the view that the physiologic mechanisms which produced death in the two groups were probably not the same. If the animals which died from the effects of less concentrated solutions succumbed to the bulk of the fluid injected, the animals which died from the effects of more concentrated solution probably succumbed to osmotic derangements.

Survival experiments in which just sublethal amounts of 1 per cent solutions of sodium chloride were administered apparently demonstrate that the pathologic changes just described are all reversible up to a sharp end point beyond which death inevitably occurs. If the infusion is stopped at any stage prior to the actual onset of death, the animal invariably recovers completely. If representative animals are killed at various intervals during the period of recovery, which lasts twenty-four hours or slightly longer, the changes in the various tissues and organs are seen to be progressively disappearing. At the end of about twenty-four hours all tissues and organs appear normal again, and no vestige of the former gross changes is to be observed.

At the risk of anticipating confirmatory physical and chemical evidence, it is suggested that after the massive infusion of essentially isotonic saline solutions death is due to no single factor. In such cases the cause of death is therefore not to be found in changes in any particular organ or system. Death probably results, rather, from a generalized physiochemical imbalance, the exact nature of which it is at present impossible to determine. It seems likely that normally reversible changes of a diffuse nature are gradually pushed further and further when the rate of infusion greatly exceeds the rate of excretion. Ultimately the organism is more or less suddenly overwhelmed, and death comes as a widespread physiochemical collapse.

This was the opinion of Dastre and Loye,[3] who concluded that tolerance to large intravenous infusions depended primarily on the rate of injection. If it did not exceed the combined capacities of the emunctories and the mechanisms for storage, part of the injected fluid was excreted, and the rest remained in the tissues. In such a case, they declared, accommodation was complete, and the net result was nothing more than a washing of the blood, a *lavage du sang*. When, on the contrary, the rate of injection was excessive, the emunctories could no longer increase their rate of elimination to such an extent as to keep pace with it. When this occurred, accumulation in the tissues soon exceeded the capacity for physiologic storage, and ultimately mechanical effects due to the inflow of the fluid overwhelmed the animal.

Before the discussion proceeds to other matters, the subject of accidental or adventitious death should receive some special consideration. Unless certain precautions are observed and sometimes in spite of the observance of these precautions, animals may succumb as the result of much smaller intravenous infusions of entirely compatible fluids. This is likely to occur particularly when solutions are hypertonic and when rates of injection are rapid.

The most frequent cause of these accidental or adventitious deaths is vomiting or regurgitation under conditions in which the swallowing reflex is abolished or obtunded. Under such conditions the regurgitated material may never appear at the mouth to give a hint of what is actually happening, and the usual convulsive muscular movements of the vomiting act may be in abeyance. Death occurs, nevertheless, because of aspiration of the regurgitated material into the respiratory tract, and the animal drowns in its own secretion. Doubtless the activity of the bronchial, pulmonary and salivary secretory mechanisms under the stimulation of intravenous infusion acts as a predisposing cause of this suffocation. Perhaps also the acidity of the gastric secretion which is inspired as a result of regurgitation is important as a precipitating cause. At all events, autopsy of an animal which has died for no apparent cause

during intravenous infusion almost invariably reveals the trachea and both bronchi full of frothy mucous and gastric secretion. Rarely frothy exudate appears at the nose and mouth before death; it can almost invariably be expressed mechanically after death by squeezing the exposed lungs. Two facts sufficiently confirm this statement of the cause of death: 1. If preliminary tracheal cannulation is performed death does not occur, in spite of the fact that such a procedure presumably does not interfere with the tracheal, bronchial and pulmonary secretory mechanisms. In short, death does not occur as a result of pulmonary edema as such. 2. If records of blood pressure and respiration are traced in animals not subjected to preliminary tracheal cannulation, they always show that such deaths are shortly preceded by the increased respiratory excursions and the profound depression of blood pressure which are characteristic of occult vomiting.

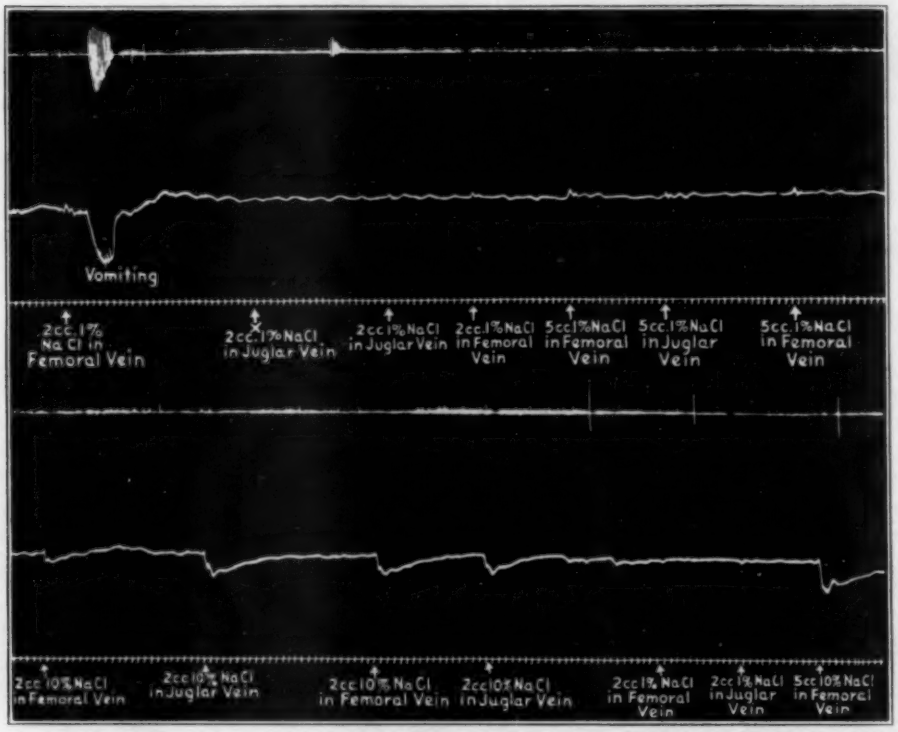
We are convinced that this is the explanation of some of those sudden deaths which occur during infusions. Such deaths previously have been assigned to other causes; thus Hirshfeld, Hyman and Wanger [4] described under the title of "speed shock" a condition which seems to fall within this category. They stated, as a result of a series of experiments, that the condition of speed shock could be produced by introducing intravenously as little as 1 or 2 cc. of solution, provided the solutions were introduced by hypodermic syringe and needle "as rapidly as the plunger could be pressed." The reaction which they described occurred within from forty to sixty seconds and included salivation, vomiting, diarrhea, dyspnea, muscular atony or at times muscular spasm and incoagulability of the blood. It was preceded by or associated with abrupt depression of the blood pressure. "At one time or another . . . in whole or in part" they were able to produce the condition with a wide variety of substances in solution as well as with insoluble substances, though "inconsistency and inconstancy" of symptoms were the rule.

In spite of many trials we have never been able to produce this phenomenon by using essentially isotonic solutions of sodium chloride, even in 10 cc. amounts and violently forceful injections. Hypertonic solutions, however, especially after animals have already received considerable amounts of fluid, are very likely to produce the vomiting reaction which we are convinced is the basis of the phenomenon. Presumably many of the substances used by Hirshfeld and his co-workers are particularly likely to stimulate the vomiting reflex.

Incidentally, it may be of interest to note that workers like Dastre and Loye [3] who have extensively employed rabbits in their experimental

4. Hirshfeld, S.; Hyman, H. T., and Wanger, J. J.: Influence of Velocity on the Response to Intravenous Injections, Arch. Int. Med. **47**:259-287 (Feb.) 1931.

work are not likely to have noted the phenomenon, for rabbits have a poorly developed vomiting mechanism. Experimenters who perform preliminary tracheotomy do not see death from this cause for the obvious reason that tracheotomized animals cannot inspire what they regurgitate. Furthermore, if the vomiting mechanism is not productive of actual regurgitation death does not ensue, and the only result is transitory hyperpnea and depression of the blood pressure, which would correspond to nonfatal "speed shock" (fig. 2).


Vomiting
2cc 1% NaCl in Femoral Vein
2cc 1% NaCl in Juglar Vein
2cc 1% NaCl in Juglar Vein
2cc 1% NaCl in Femoral Vein
5cc 1% NaCl in Femoral Vein
5cc 1% NaCl in Juglar Vein
5cc 1% NaCl in Femoral Vein
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2cc 10% NaCl in Femoral Vein
2cc 10% NaCl in Juglar Vein
2cc 1% NaCl in Femoral Vein
2cc 1% NaCl in Juglar Vein
5cc 10% NaCl in Femoral Vein

Fig. 2.—A series of attempts to produce "speed shock" by forcefully introducing small amounts of saline solution into the circulation. The very first injection (2 cc. of 1 per cent solution of sodium chloride) was followed by vomiting—extreme upper left corner. This was accidental, as indicated by the fact that repetitions of the same dose, injections of larger amounts of the same solution, and injection of small amounts of various hypertonic solutions failed to elicit the phenomenon a second time. Very hypertonic solutions (see lower panel) do produce variable momentary reductions in the blood pressure.

It is important also to avoid "pyrogenic" products in the distilled water employed in the compounding of solutions for injections and contamination of the paraphernalia used in such injections by "pyrogenic substances." The role of these substances in the production of post-

infusion reactions has been investigated by Rademaker,[5] following the lead of Seibert.[6] Although the only precaution against the inclusion of pyrogenic substances in our solutions has been fresh single distillation of water through an ordinary laboratory still and immediate sterilization by boiling, we have only occasionally encountered effects attributable to such a factor. On several occasions, however, we have attempted the use of solutions which had previously stood in the laboratory for several days under conditions which were compatible with the development of pyrogenic substances and have encountered deaths attributable to no other cause that we could determine. The use of a freshly and accurately compounded solution has obviated all difficulty from this source. On this basis we are convinced, though admittedly on insufficient evidence, that the possible presence of pyrogenic substances in infusions given to laboratory animals cannot be overlooked with impunity.

TRANSLOCATION OF WATER AND CHLORIDES

A moment's preliminary consideration of the wide fluctuations in the intake of water to which the body is accustomed should lead one to expect a well developed and probably complex mechanism for its translocation after absorption.

It should be emphasized that ordinarily water is not rejected by the gastrointestinal tract, regardless of the quantity consumed. On the contrary, all the water taken by mouth is rather speedily absorbed into the blood stream. Exceptions to this rule occur, first, when the absorbing surface of the intestine, mainly the small intestine, is the seat of some inflammatory process which interferes with its normal function. This condition produces those diarrheas which are due to abnormal products of digestion or to the presence of bacteria and their toxins. In the second place, exceptions occur when there is a disordered blood supply to the intestine, for example, in ileus. Finally, exceptions occur rarely when huge quantities of water are ingested.

That the body is capable of absorbing large quantities of water without necessarily suffering therefrom is amply demonstrated in cases of diabetes insipidus, in which the daily absorption may amount to as much as 8 to 10 liters or more over long periods. Apparently as long as the elimination keeps reasonable pace with the intake no symptoms develop.

That the absorptive surface of the intestine does not refuse water even when the latter is presented in harmfully large quantities has been

5. Rademaker, L.: The Cause and Elimination of Reactions After Intravenous Infusions, Ann. Surg. **92**:195-201, 1930; Reactions After Intravenous Infusions: A Further Study on Their Elimination, Surg., Gynec. & Obst. **56**:956-958, 1933.

6. Seibert, F. B.: Fever-Producing Substances Found in Some Distilled Waters, Am. J. Physiol. **67**:90-104, 1923.

observed by a number of investigators, Priestley,[7] MacCallum and Benson,[8] Miller and Williams[9] and Amberg and Austin.[10]

Rowntree[11] first duplicated the symptoms of water intoxication—asthenia, muscular irritability, convulsions, salivation and ultimately death—in a series of animals by administering large quantities of distilled water by mouth. He was able to relieve the symptoms both by administering saline solution and by trephining the skull. From this he concluded that the cause of death was edema, especially edema of the brain.

Helwig, Schutz and Curry[12] recently reported a clinical case in which they believed the death of a 50 year old woman was caused by absorption of some 9,000 cc. of tap water from the bowel within the first thirty hours after an operation for gallstones. In a series of 7 healthy young rabbits these authors were able to produce water intoxication and death by the repeated administration of 50 cc. of tap water by rectal catheter at intervals of thirty minutes. The first indication of water intoxication was the appearance of salivation after about 500 cc. of water had been given. This was followed by fine fibrillary twitchings of the ear and muscles of the extremities after the administration of about 600 cc. After about 700 cc. had been administered clonic convulsions and marked opisthotonos developed; these signs were associated with dilatation of the pupils and decreased urinary output. Death ultimately occurred in a generalized convulsion. These authors believe that the cause of death in water intoxication is cerebral edema, though Smyth, Deamer and Phatak[13] in 1933 explained water intoxication on the basis of alkalosis and loss of chlorides.

Of course it is a matter of everyday observation that increasing the intake of water increases the output of urine, and it is also a truism to remark that ultimately elimination must balance intake. The point

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7. Priestley, J. G.: The Regulation of Excretion of Water by the Kidneys, J. Physiol. **1**:304-311, 1916.

8. MacCallum, J. B., and Benson, C. C.: On the Composition of Dilute Renal Excretions, J. Biol. Chem. **6**:87-104, 1909.

9. Miller, J. L., and Williams, J. L.: The Effect on Blood Pressure and Nonprotein Nitrogen in the Blood of Excessive Fluid Intake, Am. J. M. Sc. **161**:327-334, 1921.

10. Amberg, S., and Austin, R. S., cited by Rowntree.[11]

11. Rowntree, L. G.: (*a*) Water Intoxication, Arch. Int. Med. **32**:157-174 (Aug.) 1923; (*b*) The Effect on Mammals of the Administration of Excessive Quantities of Water, J. Pharmacol. & Exper. Therap. **29**:135-159, 1926.

12. Helwig, F. C.; Schutz, C. B., and Curry, D. E.: Water Intoxication: Report of a Fatal Human Case, with Clinical, Pathologic and Experimental Studies, J. A. M. A. **104**:1569-1575 (May 4) 1935.

13. Smyth, F. S.; Deamer, W. C., and Phatak, N. M.: Studies in So-Called Water Intoxication, J. Clin. Investigation **12**:55-65, 1933.

is that elimination certainly does not occur at equal pace with absorption under ordinary conditions but at first definitely lags behind it. Ultimately, therefore, if a balance is to result, the rate of elimination not only must equal the rate of intake but must exceed it, in order to counterbalance the initial lag. In the meantime, no less certainly, the tissues of the body must accommodate the excess of water.

That simple dilution of the blood stream is not the only mechanism involved in the storage of water is almost axiomatic. Indeed, all clinical and experimental observers agree that a portion of any considerable amount of water added to the blood stream almost immediately leaves the circulation, lodging temporarily in the fixed tissues. This is true whether the water is absorbed into the blood stream from the gastrointestinal tract or is artificially added by direct infusion of a watery solution. Clinically, such an egress of water from the blood stream to the fixed tissues of the skin and to the subcutaneous connective tissue is recognized as edema. It shows the elementary physical sign of "pitting on pressure." One would certainly surmise, even though no experimental or other evidence were available, that the skin and subcutaneous tissues are not the only tissues involved. As a matter of fact, there is much evidence that other tissues are actually involved.

It is universally agreed that after the infusion of considerable quantities of saline solution the blood volume does not long remain augmented but tends soon to return to normal. Unfortunately there exists at present no really satisfactory and accurate method of measuring the true total volume of the blood, or the true volume of either of its two constituent parts, the plasma or the cells. This is because no known method is capable of differentiating between changes due to vasomotor adjustments and changes due to transfer of fluid to or from extravascular spaces. The methods based on the use of dye are, of course, subject to gross errors, due most probably to the influence of the vasomotor mechanism on the distribution of the dye.

Simple dilution of the blood and consequent increase in its circulating volume are the first changes that follow the addition of fluid to the blood stream. Almost immediately these changes begin to be compensated by vasomotor changes tending to augment the cubic capacity of the circulatory system. As soon as dilution of the blood has occurred to any appreciable extent, however, osmotic and other relationships are undoubtedly upset. Mechanisms are then brought into play which effect a redistribution of electrolytes between the blood stream and the tissue spaces. Thus three essentially different compensatory mechanisms are operative almost immediately after an intravenous infusion has been started. To these, moreover, is very soon added a fourth, the elimination of water and salts by the kidneys and the other emunctories.

In the absence of any accurate method for examining these several mechanisms individually, conclusions as to their interrelationships and relative importance must be somewhat conjectural. Large or even huge intravenous injections fail to produce sustained elevation of the blood pressure. Moreover, the ordinary methods of computing the total blood volume fail to show an increase for moderate additions of inorganic solutions to the blood stream. Accordingly, investigators in general believe that the escape of most artificially introduced solutions from the actual blood stream is rapid.

Thus Dastre and Loye [3] as early as 1888 computed experimentally that 75 per cent of fluids intravenously injected in large quantities passed after a short time into the tissue spaces and serous cavities of dogs and rabbits. They adduced evidence that the tissues can store with impunity amounts of such fluids equal to from one tenth to one quarter of the total body weight.

MacCallum [14] in 1904 obtained up to 15 per cent of fluids intravenously injected in large volumes into experimental animals from a cannula tied into the lumen of the intestine. He thus apparently demonstrated the importance of the intestine as a water emunctory under unusual conditions.

Bogert, Underhill and Mendel [15] in 1916 concluded as a result of experiment that the blood volume returned to normal within thirty minutes after the injection of a quantity of saline solution equal to its computed total and within so short a time as five minutes when smaller volumes were injected.

Smith and Mendel [16] in 1920 injected into rabbits an amount of fluid equal to the computed normal volume of blood and observed that the bulk of the injected fluid had left the blood stream within the first five minutes. They expressed the belief that the loss of this amount of fluid could not be explained on the basis of passage of water into the muscles or cellular tissues. It must, therefore, they stated, have been extravasated into the serous cavities, the stomach and the intestine, so far as it was not excreted in the urine.

Until much more is known about the normal movements of water and chlorides in the body, and especially about the forces concerned in the movement of water between the vascular tree and the extra-

14. MacCallum, J. B.: On the Action of Saline Purgatives in Rabbits and the Counteraction of Their Effect by Calcium, Am. J. Physiol. **10**:101-110, 1904.

15. Bogert, L. J.; Underhill, F. P., and Mendel, L. B.: The Regulation of the Blood Volume After Injections of Saline Solutions: Studies of the Permeability of Cellular Membranes, Am. J. Physiol. **41**:189-218, 1916.

16. Smith, A. H., and Mendel, L. B.: The Adjustment of Blood Volume After Injection of Isotonic Solutions of Varied Composition, Am. J. Physiol. **53**:323-344, 1920.

vascular spaces and between the intracellular spaces and the extracellular spaces, the ultimate significance of the portion of our experimental observations about to be described will necessarily remain in some doubt.

We have, however, estimated the distribution of water and chlorides in many of the soft tissues after the administration of an amount of 1 per cent solution of sodium chloride almost, but not quite, sufficient to cause death. The injection was stopped and the animals killed at the first suggestion of the precipitous decline in blood pressure which experience had shown immediately preceded death when an infusion was fatally large. Tissues were removed for analysis thereafter, as rapidly and gently as possible in order to minimize the factor of postmortem translocation of fluids and salts. At the same time all possible precautions were taken to prevent mechanical redistribution of blood from organ to organ or mechanical draining away of blood from cut surfaces.

The water content of the tissues was determined by drying excised, accurately weighed, minced tissues to constant weight in an oven at a temperature of 125 C.

It should be emphasized at this point that the condition of the tissues and organs which were analyzed for water and salt content was not necessarily incompatible with continued life. Though the condition was that which exists just preceding death, it was nevertheless one from which full and complete recovery is possible if the infusion is stopped exactly at this point. Repeatedly animals subjected to infusions of similar or almost similar magnitudes have recovered when the infusion has been interrupted just short of a presumably fatal dose.

As Skelton[17] has shown, and as appears from table 2, the water content and the mass relative to body weight of the various tissues in man and in the cat are closely similar. Presumably, therefore, similar changes in distribution of water occur in both species after massive infusions.

We have used the figures quoted by Skelton representing the weight of each organ in percentage of the total body weight, except for the various parts of the gastrointestinal tract. In this case we have used our own figures, for we have found no values in other sources. We have derived our own figures also for the normal water content of the tissues and organs, including the several portions of the gastrointestinal tract.

Our values for the gastrointestinal tract are based on analyses of 12 control cats. From these we removed the small intestine, the large intestine and the stomach. Having weighed these organs, we computed the relative weights with respect to the total body weight and thereafter

17. Skelton, H.: Storage of Water by Various Body Tissues, Arch. Int. Med. **40**:140-152 (Aug.) 1927.

determined the normal water content. In table 3 is summarized the relationship of the weights.

In table 4 are summarized the changes in water content of a number of tissues and organs after the infusion of a 1 per cent solution of sodium chloride in just sublethal amount. The figures presented in the first

TABLE 2.—*Water Content and Mass Relative to Body Weight of Various Tissues in Man and the Cat*

Organ	Percentage of Water in Organ by Weight		Weight of Organ in Percentage of Total Body Weight	
	Man	Cat	Man	Cat
Skin	72.03	68.3	18.0	13.94
Muscle	75.67	74.5	41.7	45.36
Skeleton	22.04	32.8	15.9	12.67
Brain	74.84	78.0	2.01	1.04
Liver	68.25	67.9	2.26	2.96
Heart	79.21	78.46	0.47	0.37
Lungs	78.96	76.3	0.69	0.51
Kidney	82.68	75.3	0.37	0.81
Spleen	75.77	78.2	0.18	0.28
Blood	83.00	86.7	4.90	4.46
Intestine	74.54	78.3	1.81	3.80

TABLE 3.—*Weight of the Separate Portions of the Gastrointestinal Tract Relative to the Total Body Weight in Cats*

Cat Number	Body Weight	Percentage of Body Weight		
		Stomach	Small Intestine	Large Intestine
1	2,610	1.30	3.32	0.58
3	2,590	1.08	3.87	0.55
4	2,680	1.41	4.80	0.92
5	2,900	0.97	2.90	0.71
6	3,010	1.16	4.50	0.61
7	3,180	0.99	2.86	0.64
8	2,380	1.48	3.70	0.94
9	2,480	0.82	2.86	0.55
10	2,480	1.49	4.24	0.75
11	2,540	1.05	3.45	0.67
12	2,760	0.76	2.63	0.63
13	1,860	0.83	3.44	0.73
Mean percentage of body weight		1.11	3.55	0.69
Mean percentage of body weight represented by the whole gastrointestinal tract			5.35	

* This table shows great variation in the weight of all three parts of the gastrointestinal tract, stomach, small intestine and large intestine, expressed as percentage of the total body weight. In individual cases the values vary from as much as 30 per cent below to as much as 30 per cent above the mean for the entire group.

column are our own and are therefore not identical with the values quoted in table 2, though it will be noted that the agreement is very close.

As previously stated, the figures given in table 4 represent the distribution of water after virtually maximal intravenous infusions. It is a question whether this distribution of water is characteristic after infusions of various magnitudes or only after extremely large infusions. We have no direct evidence, but comparison of our results with those of Skelton, who estimated the distribution of water among some of these

tissues after the intravenous administration of much smaller amounts of 0.9 per cent solution of sodium chloride, shows that the order of the tissues when arranged according to their increase in water content is essentially the same for the smaller and the larger infusions. This is shown in table 5.

TABLE 4.—*Change in Water Content of Organs After Massive Infusion of 1 per Cent Solution of Sodium Chloride*

Organ	Normal Percentage of Water	Percentage of Increase in Water After Infusion
Brain	78.7	— 3.9 (decrease)*
Spleen	77.8	10.0
Skeletal muscle	75.0	18.4
Cardiac muscle	76.8	21.0
Duodenum	77.8	29.0
Liver	70.3	29.0
Kidney	76.6	43.5
Skin	57.0	57.0†
Lung	79.5	111.0
Pancreas	73.9	109.0
Salivary glands	72.0	119.0
Colon	77.0	215.0
Stomach	77.0	254.0

* Under the conditions of the experiment it is questionable whether a variation of 3.9 per cent, as in the water content of the cerebrum, is significant. Nevertheless, being in the direction of decrease rather than increase, it makes it possible to state with some confidence that the cerebral tissue does not store water.

† The value for water in the skin is uncertain; not only is there a considerable normal variation in the water content of this tissue, but its fat content introduces a sizable error. The presence of fat operates to minimize any actual increase in water content, for on drying the fat does not evaporate. It thus adds to the ultimate weight of the dried tissue even though it has been entirely passive with respect to ability to hold water. The value recorded—57 per cent—was computed on the same basis as those for the other tissues. The tissue's fat content was disregarded, all possible care being exercised not to include any gross particles of fatty tissue.

In 5 cases values for water were calculated for the same animal both before and after infusion. The increase of water averaged 49.5 per cent, but this figure was not corrected for fat content.

In 2 cases in which the fat content was excluded by preliminary extraction of the tissues with ether the increase of water amounted to 38.8 per cent. In these 2 cases, however, there were no normal values as controls for the individual animals used.

TABLE 5.—*Percentage of Increase in Water Content of Organs After Large and Small Infusions of Solution of Sodium Chloride*

After Massive Infusion (500 Cc. or More per Kg. of Body Weight)—Cutting et al		After Smaller Infusion (20 Cc. per Kg. of Body Weight)—Skelton	
Blood	102	Blood	27.7
Skin	57	Skin	4.5
Liver	29	Liver	4.3
Cardiac muscle	21	Muscle	0.0
Skeletal muscle	18		

Although the magnitude of water stored increases with the size of the infusion as one would expect, the four tissues for which data are available store water in the same relative order. This would seem to indicate that each of these particular tissues, at least, shows a characteristic capacity for storing water, which increases to relatively the same extent in each case as more and more water is supplied.

Perhaps the gastrointestinal tract is an exception to this rule. Skelton [17] observed that it increased its water content by only 1.9 per cent after the smaller infusion which he used. He did not state, however, which portion of the tract was used for actual analysis. As has been previously explained, we were guided by differences in the gross appearance of the various portions of the tract at autopsy. We accordingly determined the values for separate portions of the tract and observed that the behavior of the stomach and colon differs markedly from that of the small intestine. The stomach and colon contain or store water in large amounts, whereas the small intestine contains or stores relatively little. If Skelton's figure for the gastrointestinal tract represents the small intestine only, this fact may be cited as another instance of close correlation between our findings and his. It then offers further evidence that the various tissues show characteristic behavior in the amount of water they store or contain, regardless of the absolute amount injected.

If, on the other hand, Skelton's figures represent the average capacity for storage of the gastrointestinal tract as a whole, our figures for the stomach and the colon are very much out of line. Such an interpretation would suggest that these tissues show an increasing affinity for water as the amount of infused solution increases. If the latter hypothesis is correct, there is a strong presumption that the stomach and colon take up the added water as a step in a process of excretion into the lumen of the intestinal canal, which thus acts as a safety valve. Certainly the fact that massive infusions frequently produce copious vomiting and watery purging may be considered to lend support to such a hypothesis.

The fact that the cerebrum definitely stores no water is of particular importance in view of the opinion of some investigators that when death results from water intoxication its immediate cause is cerebral edema.

Rowntree [11a] noted that cerebral edema was an outstanding feature in experimental animals in which water intoxication had been produced. The convulsive seizures and ultimate death of such animals could be prevented, he found, by decompressing the brain by means of openings made with a trephine in the skull.

Helwig, Schutz, and Curry [12] based their opinion that the dramatic features of water intoxication were due to cerebral edema largely on microscopic changes in the tissue. These changes were confined to the lungs, liver, brain, kidneys and bowel, and the most striking alteration was an acute swelling of the brain. The cerebral changes included definite widening of the perineural and perivascular spaces; vacuolation of the intercellular stroma; vacuolation, swelling and subependymal edema of the choroid plexus; vacuolation, swelling and desquamation of the ependymal lining of the ventricles, and vacuolation of the stroma of the cerebral substance.

Our observation that the cerebral substance after massive infusions does not increase its water content seems to demonstrate conclusively that whatever may be the cause of death after such infusions it is not cerebral edema. This can mean only that if the conclusions of the preceding authors are correct our animals did not die of water intoxication. Such a conclusion is not necessarily illogical, for saline solutions are not physiologically equivalent to water, even though the actual amounts of water and of saline solution which cause death may be practically identical. In all candor, however, the idea of cerebral edema as a cause of death under either set of circumstances does not seem particularly easy to reconcile with the Monro-Kellie doctrine, even in its most recently modified form.

Probably the most impressive feature observed relative to the water content of tissues after massive infusions is that it is without exception the glandular organs which show the greatest increase in water. All of these organs, the lungs, pancreas, salivary glands, colon and stomach, apparently are able to store and eliminate water against osmotic pressure gradients as at present understood. Nothing is more evident than that the distribution of water in the body after massive infusions of essentially isotonic saline solutions is not governed by any simple applications of the laws of osmosis and diffusion.

The amount of chloride in the blood and tissue was determined in these experiments by the method of Van Slyke as modified by Sunderman and Williams.[18] This method consists essentially of dissolving the tissues in a solution of potassium hydroxide, neutralizing this solution with nitric acid to the end point of methyl red, precpitating the chlorides with silver nitrate, digesting the mixture with strong nitric acid until all organic material has been destroyed and then titrating against potassium thiocyanate, using ferric alum as an indicator. All data on chlorides are reported in terms of grams of sodium chloride per kilogram of wet tissue.

Because the values for chloride in the tissues which we could find in the literature were unsatisfactory, we have computed all of our own values, both normal and after infusion. In table 6 are recorded the sodium chloride content of normal cat tissues, the sodium chloride content of these same tissues after massive infusions of 1 per cent solution of sodium chloride and the percentage of increase.

Of all the tissues, the skin shows the greatest variability in capacity for storing both water and sodium chloride. Its absolute value is intermediate among those for the other tissues of the body.

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18. Sunderman, F. W., and Williams, P. J.: The Analysis of Chlorides in Tissues, J. Biol. Chem. **102**:279-285, 1933.

Careful comparison of table 6 with table 4 shows that many of the tissues have a difference in capacity for storing the two substances. If the various tissues stored the infused solution as presented to them, viz., in the form of a 1 per cent solution of sodium chloride, the order in which the tissues appear in the two lists should be the same. The actual results are expressed mathematically in table 7.

TABLE 6.—*Normal Sodium Chloride Content of Cat Tissues and Content After Massive Intravenous Infusion of 1 per Cent Solution of Sodium Chloride*

Organ	Content in Gm. of Sodium Chloride per Kg. of Wet Organ		
	Normal	After Infusion	Percentage of Increase
Kidney	4.21	4.00	— 5.2
Liver	3.41	3.74	9.7
Lung	4.31	5.31	23.2
Duodenum	3.26	4.48	37.0
Pancreas	3.00	4.38	46.0
Skin	3.22	5.30	65.0
Muscle, cardiac	1.78	2.95	66.3
Salivary glands	2.75	4.86	76.0
Stomach	3.36	5.99	78.0
Spleen	2.51	4.86	94.0
Colon	2.69	5.58	107.0
Muscle, skeletal	1.05	2.42	130.0

TABLE 7.—*Evaluation of the Data Contained in Table 4 and Table 6 on the Assumption that Storage in the Tissues Is in the Form of a 1 per Cent Solution*

Organ	Gm. of Sodium Chloride per Kg. of Tissue		Ratio
	Theoretical	Observed	
Cerebrum	2.31	2.82	
Duodenum	4.80	4.48	1 : 1.06
Muscle, skeletal	2.60	2.42	1 : 1.08
Muscle, cardiac	3.20	2.95	1 : 1.08
Spleen	5.32	4.86	1 : 1:09
Skin	5.90	5.30	1 : 1.10
Liver	4.87	3.74	1 : 1.30
Lung	7.28	5.31	1 : 1.38
Kidney	6.00	4.00	1 : 1.50
Pancreas	6.90	4.38	1 : 1.57
Stomach	10.90	5.99	1 : 1.82
Colon	10.85	5.58	1 : 1.86
Salivary glands	11.30	4.86	1 : 2.31

As will be noted, the cerebrum acts anomalously in that it alone appears to store sodium chloride but no water. Of the remaining tissues, the duodenum, skeletal and cardiac muscles, spleen and skin store the solution most nearly in the concentration in which it is presented to them, viz., as a 1 per cent solution. Incidentally, none of these tissues are among those which take up the most water. All the other tissues store relatively far more water than sodium chloride.

ELIMINATION OF SODIUM CHLORIDE AND WATER

The effect of massive infusions of 1 per cent solution of sodium chloride is to increase the elimination of water by the water emunctories. Direct visible evidence occurs as follows: 1. Mucoid material accumulates in the tracheal cannula, showing excess secretion of the tracheal and other glands of the respiratory tract. 2. Saliva drips from the mouth, nasal secretion from the nose and tears from the eyes, showing increased activity of salivary, buccal, nasal and lacrimal glands. 3. There may be copious watery dejections from the bowels, especially if the infusion is large, showing increased secretory activity of the glands of the gastrointestinal tract. 4. Vomiting or attempted vomiting almost always occurs, probably because of stimulation by excess secretion into the stomach and upper portion of the small intestine. 5. Urine is invariably evacuated in quantity, showing evidence of increased filtration by the kidneys.

Probably the other avenues of water excretion, particularly the mechanism of sensible and insensible perspiration, are affected, though we have made no attempt to collect evidence to demonstrate such activity. Although presumably all the water emunctories contribute to the elimination of the added water of a large intravenous infusion, the actual amount eliminated by all the avenues except the kidneys is not great.

During the course of our experiments, whenever an opportunity presented itself to collect vomitus, saliva or dejections, this was done, and the volumes were measured and recorded. In a number of cases in which the volumes were sufficient, chemical analyses were made for chloride content. Such observations, however, have proved difficult to evaluate for several reasons:

1. Except for occasional cases of excessive vomiting or large dejections, the amounts of secretion which have been collected have been actually very small.

2. Animals which have neither vomited nor passed stools have recovered like other animals; though we feel sure, from autopsies performed in acute experiments on other animals, that their gastrointestinal tracts contained increased amounts of secretion during the infusion, this material must have been reabsorbed during recovery and ultimately evacuated by other channels. This phenomenon apparently shows that vomiting and defecation constitute overflow mechanisms rather than essential avenues of excretion.

3. Careful analyses of the urine eliminated during the period of recovery have shown that the kidneys eliminate virtually all the sodium

chloride and by far the largest part of the water of a massive infusion within about twenty-four hours. Actually, within such a period the kidneys may eliminate more sodium chloride than was injected, and they usually eliminate more than three quarters of all the water.

TABLE 8.—*Rate of Early Elimination of Infused Sodium Chloride and Water (During the Period of Infusion)*

Cat Number	Size of Infusion (Cc. per Kg. of Body Weight)	Time in Min.	Water Eliminated (Expressed as Percentage of Amount Infused)	Sodium Chloride Eliminated (Expressed as Percentage of Amount Infused)
2B	492	85	27.0*	....
4B	550	172	32.06	....
5B	550	156	16.0	28.0
6B	725	157	31.8*	....
7B	411	74	25.0	32.0
8B	561	130	35.0*	....
9B†	427	58	9.0	10.0
10B†	439	42	7.0	9.0
16B	545	120	2.0	4.4
17B	690	150	15.7	20.5
18B	500	120	20.0	25.0
19B‡	500	122	10.0	14.0
20B	500	124	20.0	25.3
21B	408	122	14.0	16.7

* In these animals the values were calculated on the basis of difference in weight before and after infusion; the urine was not collected.

† Animals 9B and 10B both passed copious watery stools, but the values are based solely on the urine collected.

‡ Animal 19B evacuated 130 cc. of fluid by bowel; the figures express only the elimination by kidney.

TABLE 9.—*Rate of Elimination of Infused Sodium Chloride and Water During the First Twenty-Four Hours*

Cat Number	Size of Infusion (Cc. per Kg. of Body Weight)	Time in Hours	Water Eliminated (Expressed as Percentage of Amount Infused)	Sodium Chloride Eliminated (Expressed as Percentage of Amount Infused)
5B	550	5	32	54
		20	69	95
		24.5	78	115
7B	411	5	70	95
		24	77	108
9B	427	6	47	60
		18	73	99
10B	439	5	38	48
		17	62	72
18B	500	7	47	58
		24	73	80
21B	408	7	48	59
		24	90	100

We have made a series of careful analyses of the rates of elimination of sodium chloride and water by the kidneys, which are summarized in tables 8 and 9. In table 8 appears an account of the rate of elimination of these two substances during the course of the actual infusion.

The diuretic effect of a massive infusion is shown by the kidneys within a short time after the infusion has been started, and during the actual period of administration considerable elimination occurs. During

this period the elimination of both salt and water is variable, averaging 19 per cent of all the water injected and 18.5 per cent of all the salt.

In table 9 is recorded an itemized account of the elimination of sodium chloride and water by the kidneys during the first twenty-four hours following massive infusions of 1 per cent solutions of sodium chloride.

Interesting in connection with the figures recorded in this table also is the variability of excretion of both water and sodium chloride from animal to animal, though it is by no means as great as the variability in the earlier period. The easiest explanation is to attribute such differences in rate of excretion to differences in the functioning of the kidneys, in which case we should seem to be dealing with another example of a test of renal function. We assured ourselves that the variability is actually due not to the functioning of the kidneys alone by plotting the half-hourly excretion of water and sodium chloride of three representative animals. Not only do the rates of excretion of both substances vary considerably from one half-hour to the next, but the variation is of the haphazard, unpredictable or scatter type, which indicates that the rate of excretion is governed by not one but several factors.

It is of some special interest that within twenty-four hours all the injected sodium chloride but only about 80 per cent of the water has been eliminated by the kidneys. Coller, Dick and Maddock [19] recently observed that when surgical patients were given moderate amounts of dextrose in saline solution intravenously for several days they showed a gain in weight. This was obviously due to a retention of water, though clinical edema did not necessarily appear. When the salt was omitted, even though the same amount of fluid as before was given, in the form of 5 per cent dextrose in distilled water, the retention disappeared, and weight was lost. Coller and his co-workers apparently made no determinations to discover whether the retention of water was associated with, or due to, a concomitant retention of sodium chloride; indeed, they failed even to discuss this matter at all. Most clinicians, in the absence of data to the contrary, probably would assume that the retention of water was secondary to the retention of chloride. The results we obtained by using massive doses of solutions of sodium chloride without dextrose seem to indicate definitely that retention of water is not dependent on retention of chloride. Indeed, the retention occurs at a time when the kidneys have excreted not only all the sodium chloride which was artificially injected but some of the salt previously present in the body. Half the animals excreted more than 100 per cent of the injected chloride within twenty-four hours.

19. Coller, F. A.; Dick, V. S., and Maddock, W. G.: Maintenance of Normal Water Exchange with Intravenous Fluids, J. A. M. A. **107**:1522-1527 (Nov. 7) 1936.

GENERAL ACCOUNT OF THE DISTRIBUTION AND ELIMINATION OF MASSIVE INFUSIONS OF SODIUM CHLORIDE AND WATER

If it now is attempted, on the basis of the figures already derived, to account for the entire bulk of solutions known to have been infused into the animals, the results are at first rather surprising.

The more bulky tissues of the body, muscles, skin, intestine, liver and skeleton, together account for about 80 per cent of the total weight of the cat, as can readily be computed from table 2. It may reasonably be assumed that the skeleton, which accounts for only about 13 per

TABLE 10.—*Storage of Water and Sodium Chloride in Muscles, Skin and Gastrointestinal Tract After Massive Infusions* *

	Muscle		Skin		Gastrointestinal Tract		Liver		Total	
Cat No.	Sodium Chloride	Water	Sodium Chloride	Water	Sodium Chloride	Water	Sodium Chloride	Water	Sodium Chloride	Water
2B	....	13.8	....	4.7	....	...	....	....	.....	.....
4B	14.4	10.8	11.3	14.0	2.56	7.6	....	....	.....	.....
6B	8.4	7.1	4.0	4.4	1.22	8.7	....	....	.....	.....
8B	7.3	11.3	7.9	11.0	1.44	6.9	....	....	.....	.....
16B	15.2	10.0	....	11.7	1.24	9.7	....	....	.....	.....
17B	7.6	7.2	5.3	4.4	1.46	5.5	....	....	.....	.....
Mean	10.57	10.03	7.12	8.36	1.58	7.7	1.14†	0.15†	20.41	20.24

* All values are expressed in percentage of the total amount infused.
† Derived from previous tables.

TABLE 11.—*The Abdominal Cavity as a Reservoir for Excess Sodium Chloride and Water*

Cat Number	Quantity Infused, Cc. per Kg.	Quantity of Abdominal Fluid at End of Infusion	Sodium Chloride Content, %	Percentage of Total Infused	
				Sodium Chloride	Water
1B	590	160 cc.	.....	.....	9.0
2B	492	132 cc.	.....	.....	13.4
3B	692	110 cc.	1.000	12.20	12.2
4B	550	130 cc.	0.950	7.50	7.8
6B	725	160 cc.	0.710	9.00	13.7
8B	561	140 cc.	0.835	7.90	9.5
17B	690	115 cc.	0.780	9.96	12.7

cent of the total body weight, is incapable of storing infused solutions because of its mechanical inexpansibility. On this assumption it appears that 80 per cent of the tissues of the body account for only about 20 per cent of the infused sodium chloride and only about 26 per cent of the infused water. The derivation of these values is shown in detail in table 10.

The only other tissue which might contribute any particular addition would be the blood, but it normally accounts for little more of the total body weight than the liver. Unfortunately, the ultimate volume after infusion being unknown, its contribution cannot be computed. However, actually the value would be negligible, for the simple reason that the figures already derived include the blood content of so great a percentage of the total mass of the body.

There are, of course, other possible storage places besides the fixed tissues, viz. the body cavities. That the abdominal cavity is an important storage place is indicated by the figures recorded in table 11. The thoracic cavity and the pericardial cavity contain only relatively insignificant amounts of fluid.

In the general accounting, of course, must be included the sodium chloride and water that have already been eliminated from the body by the kidneys. When all this has been done the balance sheet appears as follows:

	Sodium Chloride	Water
Percentage contained in 80 per cent of the fixed tissues of the body	19.27	26.09
Percentage contained in the abdominal cavity	9.31	11.20
Percentage excreted by the kidneys	20.30	15.90
Total	48.88	52.19

Half of the injected fluid and salt is all that can be accounted for. The remaining 50 per cent must either have been stored in the 20 per cent of fixed tissues not subjected to analysis or have accumulated in the various body cavities other than the abdominal cavity. As previously stated the gross examination of such cavities as the intestinal canal and thoracic and pericardial cavities indicates that not much of the remaining 50 per cent of the infusion could have found lodgment in these locations. The capacity of the unanalyzed 20 per cent of the tissues of the body may be much greater than at first seems logical to suppose. The distensible connective tissues about the pancreas, between the leaves of the mesentery and in the retroperitoneal space have been reported as presenting a remarkable appearance due to gelatinous edema. Doubtless other loose, areolar connective tissues throughout the body present a similar condition which is not so evident to the naked eye. Thus the subcutaneous tissues are extensive enough to contain much of the injected fluid and sodium chloride.

It is suggested that as a result of infusion the extravascular tissue spaces are distended with water and its dissolved sodium chloride. In that case this, rather than the swelling of the cells of the tissue themselves, is the important factor in the increase in size and apparent edema of the various tissues and organs. Wherever the tissues are mechanically distensible a characteristic gelatinous edema develops. In these locations, the tissues look as if they had been simply distended with water in its ordinary free-flowing form, i. e., as if they had been infiltrated by a hypodermic needle and syringe. Nevertheless, incising them reveals the existence of the water in a peculiar jellylike state, the cut surface of the tissue presenting a sticky, viscid appearance. Such a gelatinous state is said to characterize tissue fluids normally, in contradistinction to the free-flowing character of, for instance, lymph.

CONCLUSIONS

1. The lethal value for infusions of 1 per cent solution of sodium chloride in cats is of the order of 500 cc. per kilogram of body weight when the rate of injection is 5 cc. per kilogram of body weight per minute. This would correspond in a man weighing 154 pounds (70 Kg.) to 35 liters at a rate of 350 cc. per minute. Hypertonic solutions are lethal in smaller bulk and at slower rates of infusion.

2. During such massive infusions the blood pressure is neither greatly nor constantly affected. Vasodilatation and, particularly, diffusion of the solution into the tissue spaces serve to stabilize the blood pressure at an essentially normal level. At the time of death the blood pressure abruptly declines.

3. The important changes observed at autopsy are (*a*) evidences of watery vomiting and purging, (*b*) swelling of the entire animal, especially the abdomen, (*c*) the presence of a considerable amount of free fluid in the abdominal cavity, (*d*) edematous thickening of the stomach, the colon, and the urinary bladder, (*e*) gelatinous edema of the pancreas, the space between the leaves of the mesentery and the retroperitoneal space and (*f*) edema of the lungs and the salivary glands.

4. Unless pushed to a rather sharp end point of decompensation at which the blood pressure rapidly declines, infusions are not incompatible with rapid and complete recovery. The sharp end point is believed to represent some physiochemical imbalance rather than failure of any particular organ or system. Accidental death will occur in perhaps half the cases before any considerable amount of solution has been infused if precautions are not taken to prevent regurgitation, aspiration of the regurgitated material and ultimate drowning of the animal in its own vomitus. Pyrogenic substances contaminating the water used in compounding infusions may account for some premature deaths.

5. The relative weights of the various organs and tissues of the body and the water content of these tissues and organs are closely comparable as between man and the animals commonly used in the laboratory, specifically the cat. Experiments on the translocation of water following the administration of large intravenous infusions in the lower animals should therefore presumably be comparable with what occurs in man under similar conditions.

6. During and after a massive infusion both the water and the salt tend to leave the blood stream rapidly; they accumulate presumably in the tissue spaces. Relatively little water can be accommodated in such closely knit organs as the muscles and the skin, though because of their bulk their actual capacity for storage is considerable. Presumably the salt contained in the water thus stored is in essentially isotonic concentration. Organs such as the alimentary tract (except the duodenum),

the salivary glands and the lungs, which act to some extent as natural water emunctories, seem to store water differently. They probably do not store it passively in their tissue spaces as in the case of the organs previously mentioned, but actively within their parenchymatous cells, where they are preparing it for excretion. Accordingly, analyses show that duodenum, muscle, spleen and skin store sodium chloride and water in the proper proportions to make a 1 per cent solution. Liver, lungs, kidneys, pancreas, stomach, colon, and salivary glands, all organs concerned with the elimination of water, store water considerably in excess of the amount necessary to make a 1 per cent solution with their contained sodium chloride.

7. The cerebrum is the one tissue in the body which stores no water, though it seems to store some salt. Cerebral edema definitely does not occur after massive infusions of 1 per cent solution of sodium chloride and therefore cannot be the cause of death when the limits of toleration are exceeded.

8. Even during the course of the actual infusion of a massive quantity of 1 per cent solution of sodium chloride the kidneys eliminate a considerable amount of both the water and the salt. Before the infusion is complete nearly 20 per cent of both the water and the salt has been eliminated by the kidneys.

9. The amount of salt and water stored in tissues, amounting to approximately 80 per cent of the total body weight, for which analyses were available and the amount eliminated by the kidneys during the infusion equal about half of the total amount infused. The remaining half must have been stored in tissues constituting not more than 20 per cent of the total body weight. The most logical conclusion, in view of the spectacular gelatinous edema which was seen in the loose areolar connective tissues about the pancreas and in the retroperitoneal space, is that enormous quantities of water and salt are probably stored in these and other loose, areolar connective tissues throughout the body. These tissues, for obvious reasons, were not collected for analysis.

10. Within twenty-four hours after the administration of a just sublethal massive infusion of 1 per cent solution of sodium chloride all of the salt and about 80 per cent of the water have been eliminated by the kidneys. The rate of elimination is variable from hour to hour.

FAT EMBOLISM

RÉSUMÉ OF THE LITERATURE PLUS SOME NEWER THOUGHTS ON DIAGNOSIS

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Unless a subject is brought before the medical profession from time to time, it may easily slip into the background and be little thought of. Since over five hundred references to fat embolism are found in the literature, only the most striking facts concerning it will be presented in this paper. Clinically, fat embolism is difficult to substantiate conclusively. This difficulty is really not the fault of medical practitioners but is due to the nature of the disease, which makes its definite recognition difficult. Some of the newer experimental phases of its diagnosis are presented in this paper in the hope that they may be of aid to the ultimate solution of the problem.

GENERAL SURVEY

Historical Observations.—As early as 1669 Lower[1] had injected milk intravenously in dogs, and this was probably the beginning of the knowledge of fat embolism. Magendie,[2] during the years 1821 to 1836, did some experimental work on hyperlipemia and its effects on the circulation in animals. His description of the experimental introduction of liquid oil into the venous circulation is classic. Zenker,[3] in 1862, observed the first fat emboli in the pulmonary capillaries of man after a severe crushing injury to a railroad worker. The pulmonary capillaries were seen to contain a great many emboli of fluid fat. He thought that they occurred by aspiration from the stomach through the gaping hepatic veins.

Scriba,[4] in 1880, reviewed all the cases up to date and then added 34 of his own. He also conducted experiments on animals and brought forth many clinical and pathologic points which had previously been

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1. Lower, cited by Flournoy, T.: Contribution à l'étude de l'embolie graisseuse, Paris, J. B. Baillière & fils, 1878.

2. Magendie, F.: Leçons sur les phénomènes physiques de la vie, Paris, J. B. Baillière, 1827, vol. 1; 1836, vol. 2.

3. Zenker, F. A., cited by Warthin, A. S.: Internat. Clin. **4**:171, 1913.

4. Scriba, J.: Deutsche Ztschr. f. Chir. **12**:118, 1880.

obscure. Most of the discussion of fat embolism in modern textbooks is based on the statements and conclusions which he drew. However, years have shown that some of his opinions were erroneous. Fatty embolism could be regarded as causing death in only 14 of 177 cases, and in some of these he considered the cause of death doubtful.

Lehman and Moore [5] (1927) by in vitro experiments showed that histamine extracted from necrotic muscles produced a rapid disintegration of the emulsified fat of normal blood serum. They concluded that fatty embolism might be readily produced in the bone marrow on a nontraumatic basis purely by the absorption of histamine from injured tissue into the blood stream. They also showed that intravenous injections of ether produce fatty embolism of the lungs by dissolving their normal emulsified fat. When the gaseous tension of the ether was lowered by evaporation in the alveoli, the free fat became visible microscopically in the blood.

Etiology.—The experimental work done on the causation of fatty embolism has been considerable and in many instances has led to much contradiction and confusion. Men are much more frequently affected than women, the proportion being about 8 to 1. The case of the youngest patient recorded as having fatty embolism, an infant 8 months old, was reported by Ryerson.[6] The age at which the condition most commonly appears is the fourth decade of life. Rarely does it occur in children, because the fat in the bone marrow is insufficient to cause it up to the fourteenth year (Speed).[7] Landois,[8] in an excellent article on the subject, stated that he found mostly palmitin and stearin in children and infants, with a smaller proportion of the more fluid olein. At body temperature oleic acid is fluid and is more easily absorbed than the more viscous palmitic and stearic acids. For this reason fatty embolism is not so common in children. It appears that alcoholic addicts are more predisposed to fatty embolism than those not so addicted. Perhaps this is due to the instability of the emulsified fat in the serum, produced by its frequent dilution with a fatty solvent after a debauch (Cubbins—personal communication).

Lehman and Moore [5] calculated the amount of fat in the marrow of a femur and found it to be approximately 65 cc. By experimental

5. Lehman, E. P., and Moore, R. M.: Fat Embolism Including Experimental Production Without Trauma, Arch. Surg. **14**:621 (March) 1927.

6. Ryerson, E. W.: Fat Embolism in Bone Surgery: Incidence and Prevention, J. A. M. A. **67**:657 (Aug. 26) 1916.

7. Speed, K.: A Textbook of Fractures and Dislocations, ed. 1, Philadelphia, Lea & Febiger, 1916.

8. Landois, F.: Deutsche med. Wchnschr. **52**:283, 1926.

study with cottonseed oil they ascertained that if man is able to tolerate as much oil in the blood stream as a dog 120 cc. would be required for a lethal outcome. This conclusion is based on two assumptions: first, that cottonseed oil does not materially differ from the fat of the bone marrow; second, that man as well as the dog can tolerate free fat in the blood. If this is true, all the fat in the bone marrow of a femur could be well tolerated. There has been a great deal of controversy as to whether the fat is carried by the blood or by the lymph vessels. The present opinion seems to be that most of it is carried by the veins while a smaller part may be carried by the lymphatics.

It is interesting to note that experimental animals can be made to build up a resistance to experimentally induced fat embolism by repeated small injections of fat. This work was done primarily by Paul and Windholz [9] and later by Domanig.[10] They noted that such animals could withstand many times the lethal dose. No droplets of fat could be found free in the blood serum of these animals. Evidently such droplets are rapidly destroyed by a newly formed unknown substance.

Pathogenesis and Pathologic Picture.—After an injury to the fat of the bone marrow or adipose tissue, fat is liberated by the disintegration of the supporting fibrous tissue. Naturally there are ruptured blood vessels in the vicinity of the injury. The arteries squirt more blood into the area, thereby increasing the pressure, while the veins remain open and absorb the fatty mixture by venous suction (Miloslavich [11]), particularly if its consistency is more or less fluid. Gauss [12] brought out the point that fatty embolism is more common with fracture than with any other condition because the veins are encased in a bony wall. Hence they cannot collapse as elsewhere in the body but remain wide open for the admittance of the fatty mixture. This process may take place immediately or proceed for some time until coagulation occurs. This pathologic condition involves all the organs of the body and is too well known by all to be discussed in this brief résumé.

Lehman and McNattin [13] noted that fatty embolism is present in the lungs of about 50 per cent of unselected cadavers. These men have conclusively shown that anatomically the diagnosis of fatty embolism

9. Paul, F., and Windholz, F.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **38**:614, 1925.

10. Domanig, E.: Deutsche Ztschr. f. Chir. **236**:693, 1932.

11. Miloslavich, E. L.: Wisconsin M. J. **29**:139, 1930.

12. Gauss, H.: Pathology of Fat Embolism, Arch. Surg. **9**:593 (Nov.) 1924.

13. Lehman, E. P., and McNattin, R. F.: Fat Embolism: II. Incidence at Postmortem, Arch. Surg. **17**:179 (Aug.) 1928.

as the cause of death cannot be safely made. Wright [14] observed fat embolism in 52 of 100 consecutive patients examined post mortem, the majority of whom did not suffer from fracture or contusion as a result of a fall or some other accident. He also helped to substantiate the contention that postmortem observations of fat embolism are not pathognomonic evidence of violence.

Carrara [15] noted fat embolism in 22 per cent of cases of cardiovascular-renal disease and 44 per cent of cases of burn. Catsaras [16] reported fatty embolism in the lungs of 18 out of 67 patients with postinfluenzal pneumonia. To add to the already great confusion on the subject, acidosis, phlegmonous gastritis, acute pancreatitis, chronic tuberculosis, menstrual suppression, hepatitis, splenitis and tuberculous pneumonia, in fact, almost all diseases, poisonings and infections to which the body has been subjected, have been reported in the literature as having caused fat embolism at one time or another. Vance, [17] in 1931, wrote a comprehensive paper on fat embolism from a pathologic point of view, which is a classic in the present literature on the subject.

Symptoms.—There is no clinical correspondence between the apparent injury and the degree of resulting hyperlipemia. Injuries apparently identical may in one person be followed by a fatal hyperlipemia and in another cause but a slight disturbance.

The onset may be sudden, within a few hours of the injury, but usually does not become manifest until the third or fourth day. Once the symptoms set in, they may vary from a slight irritability and excitability of the patient to maniacal periods associated with high grade delirium, and death. If the symptoms are watched carefully, it is seen that they have a tendency to be cyclic. The cycle corresponds to the passage of the emboli from the pulmonic circulation to the systemic and their gradual return. Many patients with hyperlipemia appear to be doing nicely when gradually they begin to show signs of nervousness and excitability. At this time the pulse rate and temperature begin to show a slight rise. The rate of respiration shows a more rapid rise than that of the pulse, and even early in the development of the symptoms it may be dyspneic. As more capillaries are obstructed in the lungs, the dyspnea increases correspondingly. Cyanosis may or may not appear, according to the extent of pulmonary impairment. Gradually a passive congestion occurs in the lungs and moist rales are audible over the bases. A cough begins to

14. Wright, R. B.: Ann. Surg. **96**:75, 1932.

15. Carrara, M.: Friedreich's Bl. f. gerichtl. Med. **49**:241, 1898.

16. Catsaras, J.: Presse méd. **28**:618, 1920.

17. Vance, B. M.: Significance of Fat Embolism, Arch. Surg. **23**:426 (Sept.) 1931.

appear and is of a productive nature, rarely bringing up blood-stained sputum, however. For this reason, in many of the cases the diagnosis is bronchopneumonia.

As the pulmonary arterial pressure increases, the heart must beat faster in order to overcome the circulatory resistance. The pulse rate becomes faster and stronger, and the blood pressure begins to rise. If the resistance in the pulmonic circulation increases or remains great, the heart before long begins to weaken. Its rate increases while its force decreases. The blood pressure correspondingly begins to fall. If some of the emboli lodge in the coronary vessels, the cardiac failure comes on much more quickly. Before long, the pulse becomes imperceptible, the arterial pressure falls, the venous pressure rises and the picture of deep shock and cardiac failure appears. The temperature varies from subnormal to 106 or 107 F., according to whether or not the heat-regulating center is disturbed by the emboli. The usual temperature during the height of the disease is about 103 F. In the terminal stage the temperature often rises much higher.

Petechial hemorrhages (Ryerson,[6] 1916) may appear in the skin, as in any other disease in which the embolic phenomena predominate. However, because the capillaries are not actually occluded, as in bacterial endocarditis, but the circulation is greatly slowed by the increased viscosity of the blood (Gauss[18]), they are rare. LeCount and Gauss[19] reported on 14 cases of death following fatty embolism in which autopsies had been done. A study of the clinical symptoms in these cases is instructive, as it gives us some idea of what occurs in cases of milder involvement which does not have a fatal outcome.

All of the patients in these cases passed from consciousness to a restless stage. In 12 this took the form of delirium, 11 becoming so violent as to require restraint. Eleven passed from delirium to the comatose state. In all 14 dyspnea was present with an associated increase in respiratory rate, the average being 53 respirations per minute. Cheyne-Stokes respiration developed in 2 cases, air hunger in 4 and a marked cough in 2. The pulse became weak and shallow and showed an average rate of 153 per minute. Involuntary passage of urine and feces occurred in 12 cases, and in the other 2 the records were incomplete. At the time of the patient's admission to the hospital the temperature was either normal or subnormal; it then rose considerably (to an average of 105.2 F. for the 14 cases). The time that the patients lived varied from two to seventeen days, with an average of six days.

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18. Gauss, H.: Studies in Cerebral Fat Embolism, Arch. Int. Med. **18**:76 (July) 1916.

19. LeCount, E. R., and Gauss, H.: Tr. Chicago Path. Soc. **9**:251, 1915.

Diagnosis.—In the majority of cases of fat embolism the condition is so mild that it does not cause symptoms or so severe that death results in a few days from involvement of the lungs or the brain. During life the diagnosis of fat embolism is justified only if there is a history of an injury and of the typical clinical manifestations. The incubation period varies from a few hours to three or four days from the time of the accident. It is a good point to remember Dennis' rule in this respect, in spite of the exceptions: shock, three hours; fat embolism, three days; pulmonary embolism, three weeks (Speed[7]).

Additional confirmatory signs are the presence of fat in the urine, the occurrence of fat emboli in the retinal vessels as demonstrated by the ophthalmoscope and the appearance of petechial hemorrhages in the chest, shoulders and neck. The presence of the large circular cells of Elting and Martin[20] or the fat globules of Warthin[21] in the sputum is not a pathognomonic sign, as they are found in conditions other than fat embolism. As a rule, fat embolism is rarely diagnosed from clinical signs and symptoms; it is most often discovered accidentally at necropsy. In the differential diagnosis delirium tremens, fracture of the skull, bronchopneumonia and shock must be most seriously considered.

Prognosis.—The prognosis of fatty embolism should always be reserved, because some of the patients who appear to be progressing satisfactorily die suddenly. As to expectation of life, most of the patients recover, but because in only the fatal or very serious attacks is the diagnosis made and the mild attacks are overlooked, most people have the reverse opinion.

Treatment.—As fatty embolism associated with fracture is not of common occurrence and is rarely diagnosed when it does occur, one can understand why the literature on the treatment of this complication is not illuminating. Gröndahl[22] stated that a terminal result occurs in but 1 of every 3,000 cases and that death following fracture can be attributed to fatty embolism in only 1 per cent of the cases. Much experimental work has been done on the prophylaxis, with forethought and logical thinking. Wells,[23] Ryerson[6] and Caldwell and Huber[24] have shown that the use of a tourniquet during an operation or manipulation reduces to a minimum the possibility of the development of fatty embolism. This is true especially if the tourniquet is allowed to remain

20. Elting, A. W., and Martin, C. E.: Ann. Surg. **82**:336, 1925.
21. Warthin, A. S.: Internat. Clin. **4**:171, 1913.
22. Gröndahl, N. B.: Deutsche Ztschr. f. Chir. **111**:56, 1911.
23. Wells, H. G., cited by Ryerson.[6]
24. Caldwell, G. T., and Huber, H. L.: Surg., Gynec. & Obst. **25**:650, 1917.

in place for an hour after the operation. Simonds [25] observed that etherized dogs are more susceptible to fatty embolism than are those anesthetized by substances which do not dissolve fat. This is a point of some importance, and if an anesthetic which is not a solvent of fat can be used as efficiently and safely it should be given preference.

Warthin [21] advised the following prophylactic management:

1. Avoidance of unnecessary or rough handling of patients.

2. Immediate splinting and early reduction of all fractures (Tanton [26]).

3. Use of a saw in preference to the chisel in orthopedic operations, if possible (Lexer [27]).

4. Slow removal of Esmarch's bandage (Buerger [28] and Aberle [29]). Reiner [30] advised canaliculizing the vein, allowing the first blood after removal of the constrictor to flow out. Czerny [31] and fifty years later Wegelin [32] advocated intravenous injection of sodium carbonate, probably with the idea of forming a soluble soap. This method has fortunately received but little support. All experimental animals died under this regime. The active treatment of this condition is very poor, and many of the suggested methods are not only theoretically but practically in error.

Czerny [31] advised venesection to lessen the venous congestion. Schanz [33] stated the belief that physiologic solution of sodium chloride administered both intravenously and by hypodermoclysis is of benefit. Bissell,[34] however, expressed the opinion that such a procedure is contraindicated because of increased pressure on the right side of the heart. Wilms [35] suggested drainage of the thoracic duct. Fritsche [36] observed experimentally that this procedure is beneficial if done at the first appearance of the symptoms. Gröndahl [22] noted that even ligation of the femoral vein and removal of the inguinal glands did not prevent fatty embolism. Wilms [35] advised incising the area of fracture and

25. Simonds, J. P.: A Study of Low Blood Pressures Associated with Peptone Shock and Experimental Fat Embolism, J. A. M. A. **69**:883 (Sept. 15) 1917.

26. Tanton, J.: J. de chir. **12**:287, 1914.

27. Lexer, E.: Lehrbuch der allgemeinen Chirurgie, ed. 3, Stuttgart, Ferdinand Enke, 1908.

28. Buerger, L.: Vrtljschr. f. gerichtl. Med. (supp.) **39**:159, 1910.

29. Aberle, R.: Ztschr. f. orthop. Chir. **19**:89, 1907.

30. Reiner, M.: München. med. Wchnschr. **54**:2004, 1907.

31. Czerny, V.: Berl. klin. Wchnschr. **12**:593, 1875.

32. Wegelin, C.: Schweiz. med. Wchnschr. **4**:133, 1923.

33. Schanz, A.: Zentralbl. f. Chir. **37**:43, 1910.

34. Bissell, W. W.: Amount of Fat in the Blood Stream of Persons with Broken Bones, J. A. M. A. **67**:1926 (Dec. 23) 1916.

35. Wilms, M.: Semaine méd. **30**:138, 1910.

36. Fritsche, E.: Deutsche Ztschr. f. Chir. **107**:456, 1910.

combating the origin of fatty embolism by evacuating the blood and fat. Pituitary preparations, caffeine, coramine (pyridine betacarbonic acid diethylamine in a 25 per cent solution), morphine and sympatol (the tartrate of paramethylaminoethanol phenol) have been suggested in the active treatment, as they have been seen both experimentally and clinically to produce a steady fall in the quantity of fat in the blood.

VALUE OF CHEMICAL ANALYSIS OF THE BLOOD AND PHYSICAL MEANS OF DETERMINING THE QUANTITY OF FAT

Since the problem of fat embolism has to do with the presence of droplets of fat in the blood stream, it was thought that quantitative determinations of fat in the blood would be of material aid in its diagnosis. For this reason the known methods were looked up and studied in great detail. Kumagawa and Suto [37] described a saponification method in 1908. Bang [38] in 1918 described an extraction method, which however is not accurate enough to be truly scientific. Bloor, Pelkan and Allen [39] first brought the nephelometric method to the foreground in 1922. Later, in 1928, Bloor [40] published an account of an improvement on this method. Stoddard and Drury [41] described a titration method in 1929.

After a careful study, counsel was sought from several well known physiologic chemists, and all agreed that it is beyond the ability of the average part time chemist to carry out these methods with perfect accuracy. Even when the determinations are done in well equipped laboratories by properly trained men, the variations are so great as to render them of no real diagnostic value. For the present at least, the outlook along these lines is unfavorable. Clinical investigation in the serologic department of the Cook County Hospital has revealed many blood serums of almost creamlike appearance. These were from patients suffering from diabetic coma, persons with lipoid nephrosis and lactating women. In spite of the fat content of the blood having reached this startling height, these patients revealed no manifestations of fat embolism. Some investigators have noted in cases of diabetic coma that the concentration of total lipoids in the blood has reached 26 per cent (Bantin [42]), although the normal concentration is only 0.4 per cent.

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37. Kumagawa, M., and Suto, K.: Ztschr. f. Biochem. **8**:212, 1908.

38. Bang, I.: Biochem. Ztschr. **91**:224, 1918.

39. Bloor, W. R.; Pelkan, K. F., and Allen, D. H.: J. Biol. Chem. **52**:191, 1922.

40. Bloor, W. R.: J. Biol. Chem. **77**:53, 1928.

41. Stoddard, J. L., and Drury, P. E.: J. Biol. Chem. **84**:741-1929.

42. Bantin, C. F.: Diabetic Lipemia Retinalis and Fat Embolism, J. A. M. A. **86**:546 (Feb. 20) 1926.

These observations, therefore, have conclusively proved to me that it is not the total fat content of the blood in which one should be interested, but the state in which this fat occurs. If it is in the form of a stable emulsion, no fat droplets are present in the blood, and therefore no embolism can occur. On the other hand the corpuscular fat content is of all importance, as it causes the occlusion of the vessels which produces the embolic phenomena. Unfortunately, only 5 per cent of the total fat content of the blood is found in this form. If one considers that the total fat content, as has been stated before, is only 0.4 per cent, one realizes that corpuscular percentage almost approximates zero. Therefore, it stands to reason that any total chemical method for determining increases or decreases of this substance would be far beyond the scope of quantitative chemical determinations, as the percentage of error introduced by the best present day methods would be too great.

Other fields of experimental work were sought for possible aid in determining the fat content of the blood. The use of the spectroscope was suggested. However, both a physicist and an excellent physiologist stated that the concentration of fat was too small to produce any appreciable variations. At a later date the possibility of measuring electric conductivity in order to determine changes in the fat content of the blood serum was discussed. This method as well as the use of the polariscope received negative comment and was abandoned.

RESULTS OF DARK FIELD EXAMINATIONS OF THE BLOOD IN CASES OF RECENT FRACTURE AND IN CONTROL CASES

Edmunds [43] first described the dark field examination of the blood for particles of fat in 1877. Further work along these lines was carried on by Neumann [44] in 1907. Gage and Fish [45] in 1924 published a most excellent article on this subject, describing investigative work on absorption and assimilation of fat in the lower animals. The senior author was the first to give the microscopic particles of fat in the blood the name of chylomicrons (1920), meaning that they are 1 micron in diameter and are composed of chyle.

A control study of 25 miscellaneous blood serums from the medical wards of the Cook County Hospital was undertaken. No variations from the normal were found. Several creamlike specimens of blood from a lactating woman yielded a few interesting observations. In spite of a cholesterol content of 335 mg. per hundred cubic centimeters and

43. Edmunds, J.: Monthly Micr. J. **18**:78, 1877.
44. Neumann, A.: Zentralbl. f. Physiol. **21**:102, 1907.
45. Gage, S. H., and Fish, P. A.: Am. J. Anat. **34**:1, 1924.

a milky serum, no actual droplets of fat could be seen, a phenomenon which shows the marvelous stability of the emulsion of the blood serum.

As the average blood cell is 10 microns in diameter, it has been estimated that in order to occlude the finer capillaries of the lung the droplet of fat must be at least 12 to 15 microns in diameter. In none of the control cases were droplets of this size noted. In order to show the feasibility of this diagnostic method in cases of embolism, olive oil was injected intravenously into a dog. Five cubic centimeters was injected slowly. Two minutes later, with a clean syringe and needle, a cubic centimeter of blood was removed from the leg opposite to that in which the injection had been made. When a drop of this blood was examined under the dark field, ameba-shaped droplets of olive oil, at least twice the diameter of an erythrocyte, could be easily demonstrated.

TECHNIC OF ANALYSIS OF URINE IN CASES OF FAT EMBOLISM

In the study of this problem, I have examined several hundred specimens of urine for the presence of fat in suspected cases of fat embolism. After a period of time, it was observed that this apparently simple investigative phase of the problem presented an interesting physical phenomenon. Since this phenomenon heretofore has evidently not been emphasized, its investigation was undertaken. That fat is excreted by the kidneys in the urine of patients suffering from fat embolism is well known and often spoken of in the literature. But unfortunately the detection of fat in the urine is difficult because of one very elementary physical phenomenon. The droplets of fat float on the surface of the urine and therefore are not excreted from the bladder unless the last few cubic centimeters of urine are expressed. For this reason in many cases in which the urine contains fat, the specimens examined give negative results because this simple fact is overlooked. Jirka and I,[46] in 1936, conclusively showed this, both in vitro and in clinical cases. Oleic acid was injected into the pelvis of the kidney after a retrograde pyelogram had been made. It was noted several hours later that all of the injected oil could be collected from the last few cubic centimeters of urine, while the remaining 200 to 400 cc. of urine was free from fat.

A CONTROL STUDY OF THE URINE AND BLOOD OF PATIENTS WITHOUT EMBOLISM

Until Jirka and I [47] took up the study of cases of nontraumatic conditions, no investigation of the urine and blood in such cases was ever carried on. An examination of 200 miscellaneous specimens of

46. Jirka, F. J., and Scuderi, C. S.: J. Lab. & Clin. Med. **20**:631, 1935.
47. Jirka, F. J., and Scuderi, C. S.: J. Lab. & Clin. Med. **20**:945, 1935.

urine and blood in the Cook County Hospital failed to reveal a single instance of droplets of free fat in the centrifuged specimen of either the urine or the blood. Eleven of the specimens of blood showed chylous emulsion, but it was physiologic, for the blood had been drawn within an hour or two after the ingestion of a fatty meal. We next studied fluids obtained in 50 cases of fracture from one to one hundred and forty-four hours after the accident. In not a single instance were we able to find any free fat droplets in specimens of either the urine or the blood.

From the work just described it may be safe to assume that the presence of droplets of fat (larger than a chylomicron) in specimens of either the urine or the blood is indicative of free intravascular fat, which is consistent with fat embolism. However, the examination of these liquids requires long centrifuging, staining of the supernatant liquid with sudan III and careful study of the fluid. Many trials are necessary before one learns the technic.

THE VALUE OF ROENTGENOGRAMS OF THE CHEST IN THE DIAGNOSIS

In an attempt to bring further aid to the diagnosis of this condition, Jirka and I [48] proved by experimental work on dogs that roentgenograms of the chest show definite changes in the lungs after intravenous injection of oil. This work will be carried on in human beings when the opportunity presents itself. As far as I know, the roentgen ray has never been used as an aid to the diagnosis of fat embolism. For this reason I am presenting for the first time an evaluation of the use of roentgenograms of the chest for this purpose. Eleven dogs were used in the experiments, animals weighing close to 12.5 Kg. being selected whenever possible. Sterile oleic acid was given intravenously to 6 and sterile olive oil to 5 of the animals. Varying doses were used. One must not lose sight of the fact that fat embolism is not a true embolism in the sense of a permanent occlusion of a vessel. It is simply a retardation of the flow of blood through a capillary while the droplets of oil become elongated and are slowly forced from the arterial to the venous side of the circulation.

CONCLUSIONS

1. It has been demonstrated conclusively that a diagnosis of the embolism can be made during life by the use of modern diagnostic methods.

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48. Jirka, F. J., and Scuderi, C. S.: Fat Embolism: An Experimental Study on the Value of Roentgenograms of the Chest in Diagnosis, Arch. Surg. **33**:708-713 (Oct.) 1936.

2. Quantitative determinations of fat in the blood are of no value in the diagnosis, because the physiologic variations are too great.

3. Qualitative dark field examinations of the blood should be of great aid in the diagnosis, in the hands of trained microscopists.

4. In the examination of the urine in suspected cases, only the last few cubic centimeters of catheterized specimens are valuable.

5. Intravascular droplets of fat if present in sufficient quantity will always produce changes in the lungs detectable in roentgenograms.

6. Experimentally it has been shown that dogs can be made immune to many times the lethal intravenous dose of liquid fat by repeated increasing doses. Whether an emulsifying or digestive ferment develops is not clear. Although the thought is perhaps fantastic at this time, it may be said that should clinicians be able to diagnose the condition with definite accuracy, many lives might be saved by the development of an emulsifier or digestive ferment for this disease.

NORMAL ANATOMY AND VARIATIONS OF THE PERIPHERAL NERVES OF THE LEG AND FOOT

APPLICATION IN OPERATIONS FOR VASCULAR DISEASES: STUDY OF ONE HUNDRED SPECIMENS

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The treatment of obliterative vascular disease by peripheral nerve block was first reported by Silbert [1] (1922), the posterior tibial nerve having been blocked with alcohol for relief of pain in thromboangiitis obliterans. Carlette [2] (1929) reported his method of cutting the terminal sensory branches subcutaneously above a painful ulcer of the malleolus. Smithwick and White [3] (1930) reported 11 cases in which alcohol was injected and Allen [4] (1932) 29 cases from the same clinic in which similar treatment was employed. In 1933 Laskey and Silbert [5] reported on 18 patients treated by the division and immediate suture of the peripheral nerves. The procedure was recommended to avoid sloughs due to spilling or seepage of alcohol and because occasionally the entire sensory nerves were not blocked by means of alcohol. Smithwick and White [6] (1935) reported a total of 45 cases; in the later ones the block was effected by crushing the nerves rather than by injecting alcohol. The nerves were crushed for a distance of ¼ inch (0.6 cm.) if regeneration within three months was desired and of ½ inch (1.3 cm.) if anesthesia was to be prolonged for six months.

From the Daniel Baugh Institute of Anatomy, Jefferson Medical College.

1. Silbert, S.: A New Method for the Treatment of Thrombo-Angiitis Obliterans, J. A. M. A. **79**:1765 (Nov. 18) 1922.

2. Carlette, C. E.: A Rapidly Curative Operation for Irritable Ulcer of the Malleolus, Surg., Gynec. & Obst. **48**:811, 1929.

3. Smithwick, R. H., and White, J. C.: Elimination of Pain in Obliterative Vascular Disease of the Lower Extremity, Surg., Gynec. & Obst. **51**:394, 1930.

4. Allen, A. W.: Results Obtained in the Treatment of Raynaud's Disease by Sympathetic Neurectomy and in Thrombo-Angiitis Obliterans by Desensitization of Peripheral Sensory Nerves, Ann. Surg. **96**:867, 1932.

5. Laskey, N. F., and Silbert, S.: Thrombo-Angiitis Obliterans, Ann. Surg. **98**:55, 1933.

6. Smithwick, R. H., and White, J. C.: Peripheral Nerve Block in Obliterative Vascular Disease of the Lower Extremity, Surg., Gynec. & Obst. **60**:1106, 1935.

The following points have been uniformly noted:

1. The anesthetized area is also sympathectomized and the increased circulation of the part may be determined visibly, palpably and instrumentally. This increase is due to the fact that the vasoconstrictor fibers lie intermingled with the sensory components of the peripheral nerves.[7] The resultant elevations in the temperature of the surface may approach the maximum rise obtained with spinal anesthesia (Smithwick and White).

2. Pain is controlled; frequent dressings become possible; necrotic detritus may be debrided, and healing is accelerated.

3. The anesthetized area becomes dry, and loss of heat from the surface of the skin is thus diminished.

4. The procedure has reduced the number of major amputations and increased the number of minor operations and the number of patients treated successfully without operation.

5. Results have proved more satisfactory in cases of thromboangiitis obliterans than in those of arteriosclerosis.

6. A marked rise in temperature may be taken as an indication of the potential efficiency of a lumbar sympathetic ganglionectomy.

The advised operative technic consists of the exposure of the sensory nerves that supply the involved areas of the foot, one at a time and at intervals of several days to a week, through small incisions, avoiding lateral dissection of the tissues, large vessels, the use of tooth forceps, rake retractors and hemostats, and omitting suturing of the deep tissues and the fascia. Silk sutures are introduced through the skin without the aid of forceps and tied loosely with perfect approximation of the edges of the skin. In a case of thromboangiitis obliterans a careful dissection of the nerve from the remaining components of the neurovascular bundle becomes a technical difficulty.

Although impressed with the rational basis of the procedure and the enthusiastic reports of it by the previously mentioned contributors, I have noted that its application in some cases resulted in rapidly increasing necrosis and gangrene. This result was seemingly due in great part to excessive dissection necessitated by difficulty in finding the nerves, which were not located at the sites recommended by the various authors. A perusal of these authors' description reveals occasional inadequacy of descriptive detail, and from my study of anatomy I feel that in some instances slightly different approaches are preferable or advisable. A survey of many of the standard textbooks and dis-

7. Kuntz, A.: The Autonomic Nervous System, Philadelphia, Lea & Febiger, 1929.

secting manuals, English, French and German, reveals not infrequently an incongruity and inadequacy of detail in discussion of the sensory nerves of the lower extremity.

In the belief that the maximum benefit by this method is obtained only by location of the nerve with the least possible trauma, I undertook the study of (*a*) the most conservative approach for each sensory nerve of the foot and (*b*) the most constant anatomic location of each nerve at a site above the terminal (sensory) divisions and below all important motor divisions. For this investigation 70 lower extremities were carefully studied, many of which were dissected with the cooperation of members of the freshman class. The proper surgical approach and the principles suggested by these studies were applied on 30 additional specimens, so that a total of 100 lower extremities were investigated.

SAPHENOUS NERVE

Average Diameter, Course and Relations.—The average diameter of the saphenous nerve is ⅛ inch (0.3 cm.). It is the real terminal branch of the femoral nerve. It accompanies the femoral artery to the hiatus in the adductor muscle, passes along the tendon of the adductor magnus to the medial side of the knee joint and pierces the fascia lata near the tendon of the sartorius muscle. It passes downward subcutaneously behind the medial border of the tibia just posterior to the great saphenous vein, giving off the medial crural cutaneous branches to the skin of the medial and anterior surfaces of the leg. It divides into two branches, of which the smaller continues along the margin of the tibia to the ankle while the other passes in front of the internal malleolus. The latter is then distributed to the skin on the medial side of the foot and extends as far as the medial side of the great toe, anastomosing with the medial branch of the superficial peroneal nerve.

Branches and Their Variations.—In 89 of the specimens examined the nerve divided into its two terminal branches 6 inches (15 cm.) above the internal malleolus. The larger branch left the medial border accompanied by the internal saphenous vein, to cross anteriorly 4 or 5 inches (10 to 12.5 cm.) above the internal malleolus. Of the remaining 11 cases, the terminal branching occurred 5 inches (12.5 cm.) above the internal malleolus in 5, 3 inches (7.5 cm.) above in 3 and 2 inches (5 cm.) above in 3.

Sensory Distribution and Most Constant Site.—The nerve therefore supplies the surface of the medial and anterior aspects of the calf and leg and the medial surface of the instep and of the ball of the big toe (fig. 1). The most constant site was noted to be 7 inches (18 cm.) above the internal malleolus at the medial border of the tibia, posterior

or posteromedial to the internal saphenous vein and superficial to the deep fascia (figs. 2 *A* and 3 *A*).

Surgical Approach.—A 1 inch (2.5 cm.) incision is made, its center 7 inches (18 cm.) above the tip of the internal malleolus just medial to the inner border of the tibia. First the vein is located in the subcutaneous tissue, and the nerve is found directly posterior or posteromedial to it (fig. 3*A*).

POSTERIOR TIBIAL NERVE

Average Diameter, Course and Relations.—The average diameter of the posterior tibial nerve is ¼ to ⅜ inch (0.6 to 1 cm.). It is the main branch of the sciatic nerve and represents its continuation. It

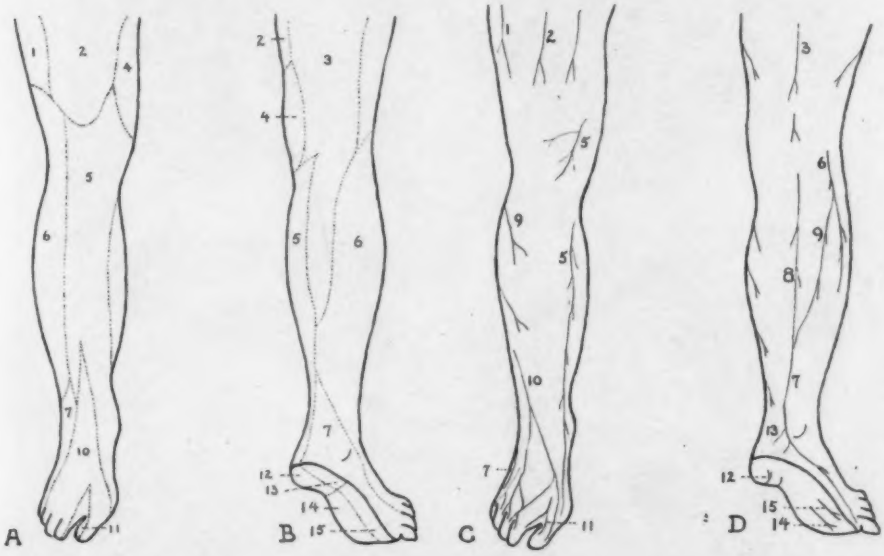

Fig. 1.—*A* and *B*, cutaneous sensory areas of the lower extremity. *C* and *D*, sensory nerve distribution of the lower extremity. The nerves are indicated as follows: *1*, lateral femoral cutaneous; *2*, anterior femoral cutaneous; *3*, posterior femoral cutaneous; *4*, cutaneous branch of the obturator; *5*, internal or long saphenous; *6*, lateral sural cutaneous; *7*, sural; *8*, medial sural cutaneous; *9*, peroneal anastomotic; *10*, superficial peroneal; *11*, deep peroneal (anterior tibial); *12*, internal or medial calcaneal rami; *13*, external or lateral calcaneal rami; *14*, medial plantar, and *15*, lateral plantar.

gives off muscular branches in the thigh and passes through the popliteal fossa, lying lateral to and behind the popliteal vein. It accompanies the posterior tibial division of the popliteal artery, lying first on its medial side and then crossing behind the artery and descending along its lateral surface. Anteriorly lie the tibialis posticus and the flexor

digitorum longus muscles, the lower part of the tibia and the posterior ligaments of the ankle joint; posterior are the gastrocnemius and soleus muscles above and the deep fascia below. Anterior to the ligamentum laciniatum, between the internal malleolus and the medial prominence

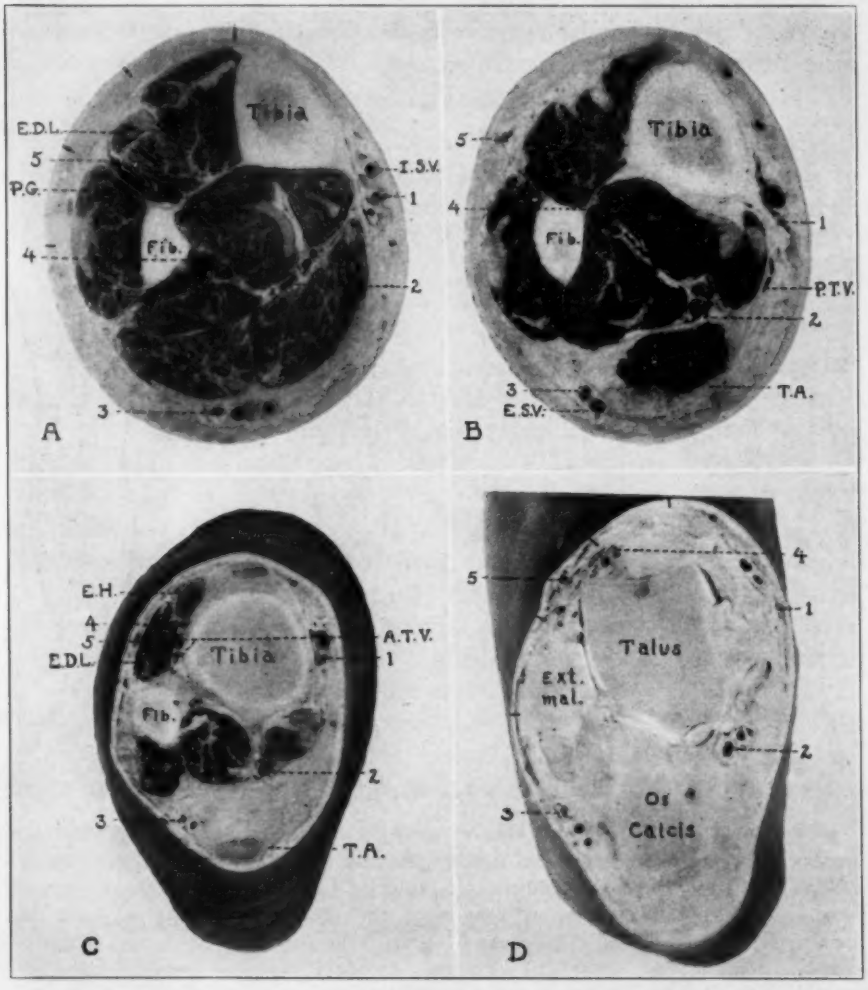

Fig. 2.—Cross sections made (*A*) 6 inches (15 cm.) above the internal malleolus, (*B*) 3½ inches (8.9 cm.) above the internal malleolus, (*C*) 1½ inches (3.8 cm.) above the internal malleolus and (*D*) at the level of the tip of the internal malleolus. The nerves are indicated as follows: *1*, saphenous; *2*, posterior tibial; *3*, sural; *4*, anterior tibial, and *5*, superficial peroneal. *I.S.V.* indicates the internal saphenous vein, *E.S.V.* the external saphenous vein, *P.T.V.* the posterior tibial vessels, *A.T.V.* the anterior tibial vessels, *E.D.L.* the extensor digitorium longus, *P.G.* the peroneal muscle group, *T.A.* the achilles tendon and *E.H.* the extensor hallucis longus. Note the superficial peroneal nerve in *A*, the saphenous nerve in *A*, the posterior tibial nerve in *B*, the sural nerve in *B* and the anterior tibial nerve in *C* and *D*.

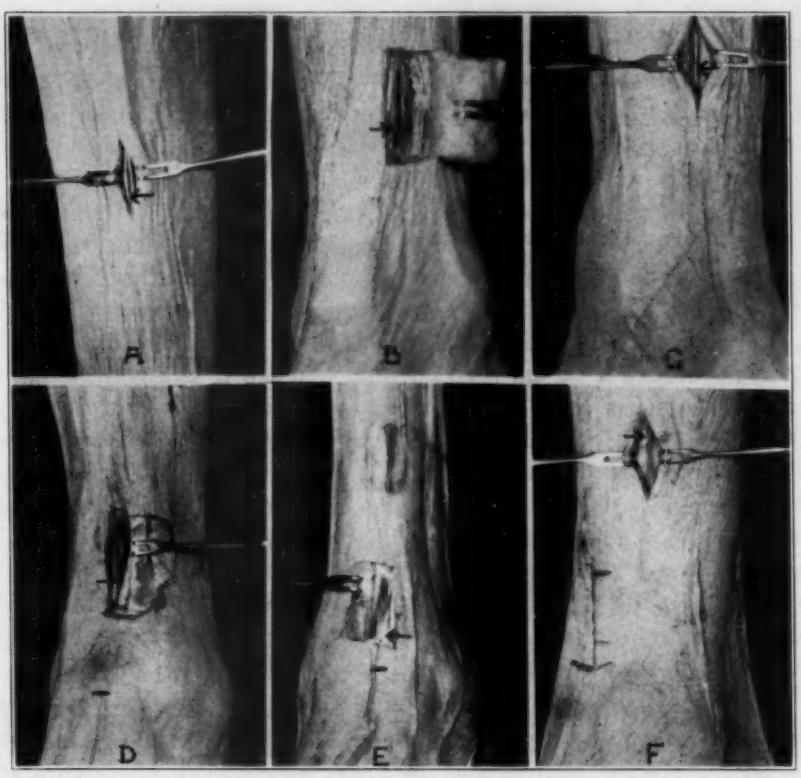

Fig. 3.—Surgical approaches to the peripheral nerves. Nerves are indicated by arrows. (The use of rake retractors and the dissection of flaps are contraindicated but practical here for demonstrative purposes.) *A*, saphenous nerve. One inch (2.5 cm.) incision made 7 inches (18 cm.) above the internal melleolus. The nerve lies posteromedial (shown to the left) to the internal saphenous vein at the medial border of the tibia. *B*, posterior tibial nerve. One and one-half inch (3.8 cm.) incision made at the medial border of the achilles tendon and 3 inches (7.5 cm.) above the internal malleolus. From lateral to medial (left to right) are the medial border of the achilles tendon, the nerve, the posterior tibial artery and venae comites and the flexor digitorum longus muscle. *C*, sural nerve. One inch (2.5 cm.) incision made at the lateral border of the achilles tendon, 4 inches (10 cm.) above the external malleolus. *D*, anterior tibial nerve. One and one-half inch (3.8 cm.) incision made 2½ inches (6.4 cm.) above the ankle joint (marked). From medial to lateral (left to right) are the tibialis anticus muscle, the anterior tibial artery, the nerve and the extensor hallucis longus and the extensor digitorum longus muscle. *E*, anterior tibial nerve. One inch (2.5 cm.) incision made 1 inch (2.5 cm.) above the ankle joint (marked). From medial to lateral (left to right) are the tibialis anticus and the extensor hallucis longus muscle, the anterior tibial artery and venae comites, the nerve and the medial tendon of the extensor digitorum longus muscle. *F*, superficial peroneal nerve. One inch (2.5 cm.) incision made anterolaterally 5 inches (12.5 cm.) above the external malleolus. The nerve lies subcutaneously in the groove between the peroneal group of muscles and the extensor digitorum longus.

of the calcaneus, the nerve divides into its plantar divisions ½ to 1 inch (1.3 to 2.5 cm.) proximal to the division of the artery.

Branches and Their Variations.—Muscular branches arise in the popliteal space and extend to the triceps surae, popliteus and plantaris muscles and to the tibialis posticus, flexor digitorum longus and flexor hallucis longus muscles below the fossa.

The terminal plantar nerves are formed ½ inch (1.3 cm.) above and behind the tip of the internal malleolus. The smaller posterior division immediately gives off the medial calcaneal branch or branches. In 4 cases this branch arose from the posterior tibial nerve directly, in 3 coming off 1 inch (2.5 cm.), and in the fourth 3 inches (7.5 cm.), above the site of terminal division. In 4 instances the posterior tibial nerve was split for a distance of 2 inches (5 cm.), 3 to 4 inches (7.5 to 10 cm.) above the internal malleolus, by a small twig off the posterior tibial artery.

The medial plantar nerve divides into muscular and cutaneous twigs and digital branches to the skin of the plantar surface of the medial aspect of the big toe and adjacent surfaces of the second, third and fourth toes. The lateral plantar division supplies the remaining part of the fourth and fifth toes by its superficial branch; the deep division gives off muscular and articular twigs.

Sensory Distribution and Most Constant Site.—The nerve therefore supplies the cutaneous surface of the medial part of the heel and the plantar surface of the foot and toes (fig. 1). The most constant site is 3 inches (7.5 cm.) above the tip of the internal malleolus, directly in the line of the medial border of the achilles tendon and at a depth of ¾ inch (1.9 cm.), anterior to the deep fascial covering of the flexor digitorum longus (figs. 2 *B* and 3 *B*).

Surgical Approach.—A 1 to 1½ inch (2.5 to 3.8 cm.) incision, its center 3 inches (7.5 cm.) above the tip of the medial malleolus, is made in line with the medial border of the achilles tendon. At a depth of ¾ inch (1.9 cm.) the fascia posterior to the flexor digitorum longus is incised and the nerve is exposed lateral to the posterior tibial artery and its venae comites, the largest component of this neurovascular bundle (fig. 3 *B*).

SURAL NERVE

Average Diameter, Course and Relations.—The average diameter of the sural nerve is ⅛ inch (0.3 cm.). Its medial cutaneous branch arises from the tibial nerve in the popliteal space, runs down the calf in the groove posterior and between the two heads of the gastrocnemius muscle with the small saphenous vein. At the middle of the leg it pierces the crural (deep) fascia, joining with the peroneal anastomotic branch of the lateral sural cutaneous nerve shortly thereafter to form

the sural nerve. The latter descends anterolateral to the small saphenous vein between the lateral third and the medial two thirds of the belly and tendon of the gastrocnemius muscle. It leaves the latter to cross behind the lateral malleolus to the dorsum of the foot.

Branches and Their Variations.—The lateral sural cutaneous nerve comes off the common peroneal nerve in the popliteal space and supplies the calf and the lateral part of the leg. The medial sural cutaneous and peroneal anastomotic branches meet any distance from the midportion of the leg to 4 inches (10 cm.), usually 6 inches (15 cm.), above the external malleolus to form the sural nerve. In only one case was the origin higher—3 inches (7.5 cm.) below the fibular head.

In 98 cases the sural nerve divided ½ inch (1.3 cm.) behind and above the tip of the external malleolus into two branches, a small posterior one, the lateral calcaneal branch, and a large anterior branch. The latter passed to the dorsum of the foot, ramified with the intermediate cutaneous division of the superficial peroneal nerve and terminated as the lateral digital branch of the fifth toe. An additional lateral calcaneal branch came off the sural nerve 2 inches (5 cm.) above the external malleolus.

Sensory Distribution and Most Constant Site.—The nerve therefore supplies the lateral surfaces of the leg, ankle, heel, foot and fifth toe (fig. 1). The most constant site is 4 inches (10 cm.) above the tip of the external malleolus just at the lateral border of the achilles tendon. Here is the external saphenous vein, and the nerve is located anterolateral to it, both lying superficial to the deep fascia (figs. 2 *B* and 3 *C*).

Surgical Approach.—A 1 inch (2.5 cm.) incision is made, its center 4 inches (10 cm.) above the tip of the external malleolus, at the lateral border of the achilles tendon. If not found immediately, the nerve will be found lying anterolateral to the external saphenous vein (fig. 3 *C*).

DEEP PERONEAL (ANTERIOR TIBIAL) NERVE

Average Diameter, Course and Relations.—The average diameter of the deep peroneal nerve is 1/16 to ⅛ inch (0.1 to 0.3 cm.). It is mainly motor. Together with the superficial peroneal nerve, it passes between the two heads of the peroneus longus and then pierces the extensor digitorum longus muscle and comes to lie in the crural interosseous space, lateral to the anterior tibial artery. In the upper part of the leg it lies between the extensor digitorum longus and the tibialis anticus muscle and in the middle of the leg, between the extensor hallucis longus and the tibialis anticus. Then it crosses behind the extensor hallucis longus, and in the lower part of the leg for 1 to 2 inches (2.5 to 5 cm.) above the ankle joint it lies between this muscle

and the extensor digitorum longus laterally. At the ankle it divides into a medial and a lateral branch.

In 95 cases the nerve lay lateral to the artery and its venae comites in the upper and middle parts of the leg, then passed anterior to the artery 4 inches (10 cm.) above the ankle joint and in the lower 2 inches (5 cm.) of the leg again lay lateral or anterolateral to the vessel. In 4 cases the nerve was lateral, then passed posterior to the artery and then medial to it, while in 1 case it lay lateral, then anterior and then medial to the anterior tibial artery.

Sabotta and McMurrich illustrated the nerve as coursing at first lateral, then posterior and then medial to the artery and its venae comites. Testut, Morris (ninth edition) and Gray (twenty-first edition) illustrated the nerve as first lateral, then anterior and then medial to the artery. As already noted, the former relation occurred in 4 cases and the latter in only 1 case, and these should not be represented as anatomic normalities but rather as infrequent variations.

Branches and Their Variations.—The nerve divides into two terminal branches. In all the cases in this series except 2 this division occurred ½ inch (1.3 cm.) above the ankle joint. In one of the exceptional cases it occurred 2½ inches (6.4 cm.) above, and in the other at the level of, the astragalotibial joint. The medial branch lies lateral to the dorsalis pedis and at the base of the first interosseous space pierces the deep fascia to supply articular twigs, muscular twigs to the first interosseous muscle and cutaneous branches to the contiguous surfaces of the great and second toes. The lateral branch supplies articular branches and muscular twigs to the extensor digitorum brevis muscle.

Sensory Distribution and Most Constant Site.—The nerve supplies only the dorsal contiguous surfaces of the first and second toes (fig. 1). The most constant site is 1 inch (2.5 cm.) above the astragalotibial joint anteriorly beneath the cruciate crural ligament, and between the extensor hallucis longus muscle medially and the extensor digitorum longus laterally. It lies lateral or anterolateral to the anterior tibial artery and its venae comites.

A less constant site is 2½ inches (6.4 cm.) above this joint, between the extensor hallucis longus muscle laterally and the tibialis anticus medially. Here the nerve lay anterior to the artery and its venae comites in 96 of the cases and posterior in 4 (figs. 2 *C* and *D* and fig. 3 *D* and *E*).

Surgical Approach.—A 1 inch (2.5 cm.) incision is made, its center 1 inch (2.5 cm.) above the ankle joint anteriorly at the juncture of the outer two thirds and medial third of the surface of the skin of the anterolateral quadrant of the leg (fig. 2 *D*). The cruciate crural

ligament is slit, the medial tendon of the extensor digitorum longus retracted laterally, the tendon and belly of the extensor hallucis longus drawn medially and the nerve exposed as it lies anterolateral or lateral to the artery and its venae comites. In 5 cases it was found medial to the artery (fig. 3 *E*).

The following, less desirable approach may be utilized if gangrene is ascending the dorsum of the foot to make the approach just described inadvisable. A 1 to 1½ inch (2.5 to 3.8 cm.) incision is made, its center 2½ inches (6.4 cm.) above the ankle joint anteriorly just lateral to the readily palpable tendon of the tibialis anticus muscle. The transverse crural ligament is slit, the tendon of the tibialis anticus retracted medially and that of the extensor hallucis longus laterally. Beneath the belly of the latter lies the neurovascular bundle on the anterolateral surface of the tibia. In this exposure the nerve was found anterior or anterolateral in 96 cases and posterior in 4. The nerve is easily lifted away from the artery, unlike the venae comites, which are bound to the vessel by tough fibrous strands (fig. 3 *D*).

SUPERFICIAL PERONEAL NERVE

Average Diameter, Course and Relations.—The average diameter of the superficial peroneal nerve is ⅛ inch (0.3 cm.). It is formed, with the deep peroneal nerve, by the division of the peroneal nerve behind the head of the fibula, after the latter nerve perforates the peroneus longus muscle. The superficial branch leaves between the two heads of the muscle and courses down the leg on its outer aspect, covered by the peroneus brevis. In the lower third of the leg it pierces the crural (deep) fascia, dividing into the medial and intermediate dorsal cutaneous nerves, which are distributed over the dorsum of the foot to the toes.

Branches and Their Variations.—The nerve pierced the crural (deep) fascia, to become subcutaneous 5 inches (12.5 cm.) above the tip of the external malleolus in 90 cases in this series. In 10 cases it exited elsewhere—6 inches (15 cm.) above the tip of the external malleolus in 1, 3 inches (7.5 cm.) above in 5, 2 inches (5 cm.) above in 2 and 4 inches (10 cm.) above in 2.

The division of the nerve into its two branches was usually found 2½ inches (6.4 cm.) above the external malleolus. In 3 cases the division occurred below and in 5 cases above this point, the highest division occurring 5 inches (12.5 cm.) above the external malleolus, at the site of exit of the nerve through the deep fascia.

The medial branch supplies the medial part of the dorsum of the foot dividing into two branches, one to the medial side of the big toe and the other to adjacent sides of the second and third toes. The inter-

mediate division supplies the intermediate portion of the dorsum of the foot, dividing into two branches. One supplies the adjacent surfaces of the third and fourth toes; the other terminates in the fourth and fifth toes and anastomoses with the sural nerve.

Sensory Distribution and Most Constant Site.—The nerve therefore supplies the anterior surface of the lower one third of the leg and the region of the ankle, the medial and intermediate parts of the dorsum of the foot and the dorsum of all the toes except the adjacent surfaces between the first and second toes (fig. 1). The most constant site is 5 inches (10.5 cm.) above the tip of the external malleolus, just within the anterior border of the fibula, in the groove between the peroneal group of muscles and the extensor digitorum longus. The nerve was found exiting through the crural (deep) fascia and lying in the subcutaneous tissues in 91 of the cases. In 9 cases the nerve was found beneath the deep fascia (figs. 2 *A* and 3 *F*).

Surgical Approach.—A 1 inch (2.5 cm.) incision is made, its center 5 inches (12.5 cm.) above the tip of the external malleolus and in the palpable groove between the peroneal group of muscles and the extensor digitorum longus. This site is at the juncture of the lateral third and the medial two thirds of the surface of the skin of the anterolateral quadrant of the leg (fig. 2 *A*). The nerve was found subcutaneously in 91 of the cases. If the nerve is not located, the deep fascia is to be incised, for it lay deeply in 9 cases (fig. 3 *F*).

CALCIFICATION AND OSSIFICATION IN TUBERCULOMA OF THE BRAIN

REVIEW OF THE LITERATURE AND REPORT OF THREE CASES

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AND
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The intracranial lesions which come to be the seat of calcareous deposits or bony formation vary remarkably in nature and location. Calcification of the pineal body and of the choroid plexus and formation of bone in the dura and in its reduplications seem to be the result of regressive change and are of no clinical importance. On the other hand, roentgenograms of the skull of a patient who has presented symptoms and signs of increased intracranial pressure or of some localized lesion occasionally disclose an abnormal shadow cast by calcareous or osseous deposits. As demonstrated in a series of over 600 cases of intracranial tumor in which autopsy was done, which were studied in the Cajal Laboratory, calcification is most likely to occur within a true neoplasm. In a few instances, however, the lesion has turned out to be of some other character, such as a calcified tuberculoma. Three examples of calcified or ossified tuberculoma which came to our attention have been made the subject of special study. Certain interesting facts pertaining to the general problem of calcification and formation of new bone, which have hitherto not been stressed, have thereby come to light. We have recorded our observations and reviewed the reported cases which we were able to find. It was our purpose to study the incidence and behavior of these healed tuberculomas, to investigate the histologic character of the calcareous or osseous deposits within their borders and to determine the possible significance of these phenomena.

Regardless of its location, the formation of a tubercle is the result of a reaction of nonimmune tissues to the tubercle bacillus or, more strictly speaking, to its waxy content. The stages through which the tubercle passes depend somewhat on the type of organism and on the ultimate degree of resistance of the host. If the disease proves

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to be rapidly progressive, the reactive phases of the tubercle—encapsulation, fibrosis, calcification and ossification—are not observed, the lesion showing only central caseation. On the other hand, when the process of healing occurs it is accompanied by some or all of these characteristic changes. These evidences of bodily reaction do not necessarily mean complete quiescence of the lesion. Local or general spread of the disease may take place within the cranial space, as elsewhere, even after more or less complete healing has taken place.

The behavior of tuberculous infection in the intracranial and intraspinal spaces varies considerably in different cases. In most instances the lesion occurs in the form of leptomeningitis. Whether in such cases the miliary tubercles represent the primary lodgment of bacilli as a result of blood stream infection (as in generalized miliary tuberculosis) or, as some have argued, a secondary spread from some preexisting tubercle is of no vital moment in this connection.[1]

In a smaller number of cases autopsy discloses one or more discrete tubercles lodged in the substance of the brain, with or without miliary tubercles in the leptomeninges. The tubercles may be small, in which case they are often multiple and at times numerous. Occasionally, however, a large solitary mass is found which is capable of provoking an increase in intracranial pressure. Patients with such a lesion not infrequently come to operation with a diagnosis of intracranial tumor, and the surgeon may be entirely unaware of the nature of the lesion until the microscope makes it clear.

Certain pathologic characteristics of tuberculomas of the brain should be emphasized. It is of interest that while they may be found in any or all parts of the brain they tend to develop in the cerebral or cerebellar cortex, probably because of the more abundant blood supply of this structure. The tendency of solitary tubercles to be situated in the cerebellum is as yet unexplained.[2] True caseation, with its characteristic softening, is never found in tuberculomas of the brain; instead there is

1. It has seemed to us that the theory that tuberculous meningitis is due to a secondary spread of infection from a preexisting tubercle lacks something to make it entirely convincing. The presence of a tubercle is not a priori evidence that the new infection has come from this source. On the other hand, the presence of cerebral tubercles of different sizes in certain instances suggests that "showers" of organisms have reached the brain on several different occasions. Further, observations in such cases do not indicate that the infection has spread concentrically about the primary tubercle, as usually happens when leptomeningitis is consequent to surgical interference with a gross tuberculoma. On the contrary, the miliary nodules are clustered primarily about the branches of the middle cerebral arteries, which strongly suggests that the organisms arrived by these channels. The subject needs further study before it can be considered closed.

2. Ehlers, H., and Courville, C. B.: Solitary Tuberculoma of the Cerebellum, Bull. Los Angeles Neurol. Soc. **1**:81, 1936.

solidification of necrotic tissue, even in the absence of fibrous connective tissue. This is perhaps a result of the peculiarities of the cerebral blood supply or the effect of some unusual reaction of the brain to the bacillus.

INCIDENCE OF CALCIFICATION AND OSSIFICATION IN TUBERCLES OF THE BRAIN

The actual incidence of calcification or formation of bone in intracranial tuberculomas must be very low. In most instances the patient dies of tuberculous meningitis or of the effects of increased intracranial pressure before calcification can take place. In other words, in most cases either the progressive character of the lesion itself or the malignant nature of the attendant meningitis precludes the possibility of those changes in the tuberculoma which favor calcification or ossification. Garland and Armitage [3] noted the incidence of tuberculoma as shown by 13,000 autopsies. Eighty-nine tuberculomas were observed at these autopsies; in 2 cases (2.51 per cent) the lesion was calcified. The incidence as observed at autopsy is therefore extremely low (0.014 per cent). In a collected series of 815 cases of tuberculoma reported in the literature, Scott and Graves [4] noted only 11 instances of calcification (1.3 per cent). The relative infrequency of these healed lesions was further stressed by Stewart,[5] who stated that examples are few and far between. Freeman [6] stated that healed tubercles are of questionable existence, although he reported 2 calcified cortical lesions which he thought might be of tuberculous origin. In a series of 1,000 cases of intracranial tumor observed in Cushing's clinic, Van Wagenen [7] found but 14 instances of tuberculoma. None of these lesions was said to be calcified.

In a survey of 13,839 reports of autopsies, Rasdolsky [8] found 32 cases of tuberculoma of the brain. In only 1 case was calcification present in a tuberculoma.

Our own figures may be of interest in this connection. In a series of 15,000 autopsy records were listed 405 cases of tuberculous meningitis

3. Garland, H., and Armitage, G.: Intracranial Tuberculomata, J. Path. & Bact. **37**:461, 1933.

4. Scott, E., and Graves, G. O.: Tuberculoma of Brain: Report of Four Cases, Am. Rev. Tuberc. **27**:171, 1933.

5. Stewart, M. J.: Healed Tuberculoma of the Cerebellum, J. Path. & Bact. **30**:577, 1927.

6. Freeman, W.: Neuropathology: The Anatomical Foundation of Nervous Diseases, Philadelphia, W. B. Saunders Company, 1933, p. 174.

7. Van Wagenen, W. P.: Tuberculoma of the Brain: Its Incidence Among Intracranial Tumors and Its Surgical Aspects, Arch. Neurol. & Psychiat. **17**:57 (Jan.) 1927.

8. Rasdolsky, I.: Tuberkulome des Gehirnes, Ztschr. f. d. ges. Neurol. u. Psychiat. **154**:18, 1935.

and 43 cases of tuberculoma of the brain. In 3 cases the tuberculomas were either calcified or calcified and ossified. The incidence of "healed" tubercles in our series would therefore be 1 in 5,000 miscellaneous cases (0.02 per cent), 1 in 135 cases of tuberculous meningitis (0.7 per cent) and 1 in about 15 cases of tuberculoma of the brain (6.6 per cent).

REVIEW OF THE LITERATURE

In a study of intracranial tumor published in 1864, Ogle [9] reported 2 calcified tuberculomas in 75 cases of calcified tuberculous lesion collected over a period of twenty-two years. Lancereaux and Lackerbauer [10] reported a case of calcified tuberculoma in the left optic thalamus; the lesion had apparently been present for over sixty years. In Foà's case [11] a calcified tuberculoma, apparently quiescent, was found in the left cerebellar hemisphere of a 12 year old boy who died of nephritis. The first case in which a diagnosis of calcified tuberculoma was made roentgenographically was that of Klieneberger.[12] The diagnosis was never verified. In a discussion of the roentgen aspects of the problem, Ström [13] described a case in which the diagnosis was verified surgically and cited the cases of Siemon [14] and Sabat.[15] Another case in which the lesion was discovered by roentgen examination (post mortem) was that described by Stewart.[5] Other cases in which the diagnosis was verified by operation or by roentgen examination were described by Marie, de Martel and Behague,[16] Cushing,[17] Paterson and Stevenson [18] and Vincent,

9. Ogle, J. W.: Cases Illustrating the Formation of Morbid Growths, Deposits, Tumors, Cysts, etc., in Connection with the Brain and Spinal Cord, and Their Investing Membranes, Brit. & For. M.-Chir. Rev. **34**:457, 1864.

10. Lancereaux, E., and Lackerbauer, M.: Atlas d'anatomie pathologique, Paris, G. Masson & fils, 1871, p. 395.

11. Foà, P.: Tubercolo cerebellare guarito, Gior. d. r. Accad. di med. di Torino **9**:403, 1903.

12. Klieneberger, Carl: Die Radiographie intracranieller Prozesse in der inneren Medizin, mit besonderer Berücksichtigung der radiographisch darstellbaren Hirntumoren, Fortschr. a. d. Geb. d. Röntgenstrahlen **14**:106, 1909.

13. Ström, S.: Ueber die Röntgendiagnostik intrakranieller Verkalkungen, Fortschr. a. d. Geb. d. Röntgenstrahlen **27**:577, 1919-1920.

14. Siemon, G. S.: Ausgedehnter Defect und teilweise verknöcherter Tumor der linken Grosshirnhemisphäre, Atrophie der rechten Kleinhirnhemisphäre und der linken Olive, Inaug. Dissert., Marburg, 1893; cited by Ström.[13]

15. Sabat: Aus der Röntgendiagnostik der Erkrankungen des Kopfes und der Wirbelsäule, Verhandl. d. deutsch. Rönt.-Gesellsch. **9**:101, 1913; cited by Ström.[13]

16. Marie, P.; de Martel, and Behague, P.: Ablation d'un tubercule intracranien: Guérison du malade, Rev. neurol. **36**:1109, 1920.

17. Cushing, H.: The Intracranial Tumors of Preadolescence, Am. J. Dis. Child. **33**:551 (April) 1927; Intracranial Tumours, Springfield, Ill., Charles C. Thomas, Publisher, 1932, pp. 114-115.

18. Paterson, J. E., and Stevenson, W. D. H.: Case of Healed Tuberculoma of the Brain: Operative Removal, with Pathological Report, Glasgow M. J. **113**: 281, 1930.

Heuyer and Vogt.[19] In all these cases the patients were reported to be alive at the time the articles were published, which speaks for complete quiescence of the lesion. The lesion was extirpated in all cases except that of Cushing, in which only suboccipital decompression was done for a cerebellar tuberculoma which subsequently became progressively calcified. In the cases of Smith [20] and of Borchardt [21] the diagnosis was verified at autopsy.

The essential details of the reported cases are included in the table.

In this series of 18 reported cases (including 3 of our own) of calcified tuberculoma of the brain, the lesion was single in 15 instances and multiple in 3. There seemed to be no site of special predilection. Diagnosis was made ultimately by autopsy in 10 cases, by operation in 6 cases and by roentgen examination in 2 cases.

The quiescence of calcified or ossified tubercles is evidenced by the patients' long periods of survival (over sixty years in the case of Lancereaux and Lackerbauer [10]) and by the fact that in 6 cases (33.3 per cent) the patient was still living at the time the report was made, from one and a half to eleven years after the condition had been diagnosed. Surgical extirpation was not followed by tuberculous meningitis, a disease which often occurs after removal of noncalcified tuberculomas of the brain. Death may result from the spontaneous development of tuberculous meningitis in such cases, however (cases of Foà [11] and Borchardt [21] and our own case 3). A fatal issue may be due also to increased intracranial pressure and exhaustion (our case 1), to internal hydrocephalus (our case 2), to status epilepticus (?) (case 2 of Ogle [9]), to Addison's disease (Stewart [5]) or to other related (pulmonary tuberculosis in our case 2) or unrelated (uremia in the case of Lancereaux and Lackerbauer [10]) causes.

REPORT OF CASES

CASE 1.—*Vomiting and left hemiplegia in a boy of 8 years; recent enlargement of the head, aphasia and progressive impairment of auditory and visual acuity; admission in coma; calcified mass in right parietal lobe shown in roentgenogram; death; autopsy; large calcified tubercle in right parietal lobe.*

A Mexican boy aged 8 years was admitted to the Los Angeles County Hospital on Jan. 13, 1931. He was then in a state of coma. The parents stated that at the age of 3 years the patient began to have attacks of headache and vomiting associated with unsteadiness of movement; these continued for four years. For the

19. Vincent, C.; Heuyer, G., and Vogt, C.: Tubercle pariéto-occipital opéré depuis 3 ans, Rev. neurol. **2**:880, 1933.

20. Smith, R. P.: Large Calcified Tuberculoma of Cerebrum with Independent Terminal Cerebral Hemorrhage, J. Path. & Bact. **30**:583, 1927.

21. Borchardt, J.: Verkalkte Solitärtuberkel im Gehirn bei tuberculöser Meningitis, Arch. f. Kinderh. **99**:181, 1933.

Author	Age	Sex	Pathologic Observations	Source of Infection	Comment
Ogle, 1864 (case 1)	36	F	Calcified tuberculoma in velum interpositum; ventricles distended, ependymal granulations; thickened arachnoid	Shoulder and lungs	Symptoms for 1 mo.
(case 2)	Child		Calcified tuberculoma size of hazelnut in right cerebellar lobe	Not stated	Epileptiform convulsions
Lancereaux and Lackerbauer, 1871	65	M	Calcareous tuberculoma size of hazelnut in left optic thalamus	Lungs	Right hemiparesis since age of 4 yr.
Siemon, 1895 (quoted by Ström)	?	?	Calcified tuberculoma 4.5 by 2.5 by 2 cm. in ventral part of frontal lobe; bony formation and calcareous crystals demonstrated histologically	Not stated	
Foà, 1903	10	M	Calcified tuberculoma deep in left cerebellar hemisphere; meningitis; slight hydrocephalus	Not stated	
Sabat, 1909 (quoted by Ström)	17	?	Calcified tuberculoma size of walnut in inferior portion of right frontal and parietal lobes	Not stated	Jacksonian fits and hemiplegia on left
Klieneberger, 1909-1910	12	M	Calcified tumor in region of corpora quadrigemina (diagnosed as tuberculoma by roentgenogram and tuberculin test)	Unknown	
Ström, 1919-1921	21	F	Calcified tuberculoma size of plum in left frontal lobe, verified by operation; calcareous material and bony formation shown microscopically	Unknown	Symptoms for 13 yr.
Marie, de Martel and Behague, 1920	18	M	Tuberculoma size of mandarin orange in left frontal lobe, verified by operation; microscopic demonstration of calcareous material in tubercle	Tuberculous glands in cervical region	Jacksonian convulsions, paralysis of right arm; alive after operation
Stewart, 1927	27	M	Calcified tuberculoma size of hazelnut in right cerebellar lobe; demonstrated by roentgenogram after death, verified at autopsy	Tuberculous glands of cervical region	Death from Addison's disease
Smith, 1927	62	M	Tuberculomas in right cerebral hemisphere and lenticular nucleus; calcareous material demonstrated microscopically	Unknown; mother died of tuberculosis	"Stroke" at 4½ yr.; dragged left foot, tremor right hand
Cushing, 1927	14	M	Progressive calcification of tuberculoma exposed at operation; not verified histologically	Pulmonary tuberculosis	Intracranial pressure; alive 7 yr. after operation
Paterson and Stevenson, 1930	16	M	Tuberculoma of right parietal lobe; calcareous material demonstrated microscopically	Not given	Convulsions at 2 and 5 yr.; mental symptoms at 13; still alive after operation
Vincent, Heuyer and Vogt, 1933	8	M	Tuberculoma size of hazelnut in right parieto-occipital region; roentgen and histologic demonstration of calcification; tissue removed at operation	Not stated; father died of tuberculosis	Symptoms for 6¾ yr.; alive 32 mo. after operation
Borchardt, 1933	7	M	Four small conglomerate tuberculomas, exact location not stated; calcification demonstrated roentgenographically and histologically	Pulmonary tuberculosis	Symptoms for 4¾ yr.; died of tuberculous meningitis
Evans and Courville, 1938					
Case 1	8	M	Large calcified tuberculoma 6 by 7.5 cm. in right parieto-occipital region; demonstrated roentgenographically before death	Pulmonary tuberculosis	Symptoms of increased pressure, aphasia and left hemiplegia for 5 yr.
Case 2	10½	M	Calcified tuberculoma 3 by 1.3 by 0.7 cm. in right frontal lobe; noncalcified tuberculoma in left cerebellar hemisphere	Tuberculous tracheobronchial lymph nodes	"Tuberculous meningitis" at 3 yr.; general convulsions at 10 yr.
Case 3	6	..	Calcified and ossified tuberculomas in right frontal lobe (1 by 0.5 cm.) and left frontal and parietal lobes (2 to 6 cm.)	Probably pulmonary tuberculosis	Listlessness and irritability for 3 wk. before death

* In all the cases the diagnosis was verified at autopsy unless otherwise stated.

past year there had been gradually progressive weakness of the left arm and leg. For nine months there had been marked increase in fluid intake and output. The patient's head had noticeably enlarged for five months. There had been rapid loss of vision and hearing for three months, and the boy had been completely deaf and blind for about two months. He had been in a comatose state for sixty hours before admission.

The child was born by precipitate delivery. Shortly before the onset of illness he sustained a minor injury to the head, which was probably of no significance. During the past three years he had acquired a peculiar antipathy for sweets.

The boy was deeply comatose. The skin, which was darkly pigmented and covered with sudamina, was tightly drawn over the emaciated trunk and extremities. There was an increased amount of hair over the body. The head was much larger than normal, the parietal bosses being particularly prominent. The occipitofrontal circumference of the head was 21 inches (53.3 cm.), and the suboccipitobregmatic circumference was 21½ inches (54.6 cm.). The percussion note was high pitched, and a well defined cracked pot sound could be elicited. The head and eyes were turned to the right. Coarse bubbling rales were heard over the entire chest. There was some lagging of the left side, associated with dulness of the percussion note on this side.

The pupils were widely dilated and reactionless. The left was slightly larger than the right. A rotatory nystagmus was constantly present. The optic disks were small and pale and presented a fairly sharp margin. The vessels were small and somewhat tortuous. The cup was filled in. The left arm and leg were rigid in a position of complete extension and internal rotation. The right arm was rigid in flexion; the right leg was less rigid and could be moved within narrow limits. The deep reflexes were entirely absent throughout. On the right Babinski's sign and Chaddock's sign were elicited; on the left the extension rigidity prevented any plantar response.

A roentgenogram of the skull taken two days after the patient's admission disclosed a calcified mass about 4 cm. in diameter in the right posterior parietal region. All the suture lines of the cranial vault were widely spread. There was marked convolutional atrophy of the inner table of the skull (fig. 1).

The child died on January 30 with signs of bronchopneumonia.

An autopsy was performed by Dr. Sidney R. Garfield twelve and one-half hours after death. Pleural adhesions were noted at the apex of the right lung and over the posterior portions of both lungs. A small caseous and calcified nodule about the size of a pea was observed at the base of the right lung. The tracheobronchial lymph nodes also were calcified and necrotic. The myocardium was flabby. The liver was congested and showed cloudy swelling. The spleen was slightly enlarged and congested. The pancreas was hard and fibrous. The bladder was distended, and the mucous membrane showed a low grade inflammation.

The skull was extremely large and the vault thin. The sutures were open, and there was an advanced degree of convolutional atrophy of the inner table.

The convolutions of the brain were markedly flattened, particularly over the dorsolateral surface of the right parietal and occipital lobes, where the cortical markings were indistinct. The cortex in this region had a gelatinous appearance. Beneath the cortex could be palpated an irregular indurated mass. The brain was sectioned horizontally through the basal ganglions and the internal capsule. In the parieto-occipital centrum was a large, irregular, firm, sharply circumscribed mass which extended almost to the surface of the brain. On cross section it measured 6 by 7.5 cm. in its greatest diameters. Near the center of the mass was a hard,

* In all the cases the diagnosis was verified at autopsy unless otherwise stated.

irregular, yellowish white calcareous mass (fig. 2). Sections were taken from this and from adjacent areas for microscopic study.

A section from the central calcareous portion of the tuberculoma disclosed an irregular shell of calcification composed of a fusion of many small crystals. The interior of the shell was structureless. This calcareous formation was surrounded by a fibrous connective tissue scar which had undergone almost complete hyalinization. In the adjacent cerebral tissue the blood vessels had become calcified, the tissue being studded with a large number of round or oval darkly stained granules. The nerve cells in the region were also "calcified,"[22] the encrusted cells still retaining to a great extent their original form.

Sections from the peripheral portion of the tuberculoma showed the typical characteristics of such a lesion: lymphocytes, plasma cells, fibroblasts and giant cells.

Fig. 1 (case 1).—Roentgenogram of the skull, showing the calcareous mass in the right parietal region. The thinned cranial vault with increased convolutional markings, separation of the suture lines and erosion of the dorsum sellae are all indicative of long-continued increased intracranial pressure.

Comment.—This case presents a number of unusual features. The long, continuous course suggests the progressive growth of the tuberculoma. This is further suggested by the characteristic structure of the peripheral portion of the tuberculoma. One might predicate another possibility, however: that a recurrence of activity had occurred in the peripheral portion of the tuberculoma after its central portion had

22. The incrustation of nerve cells with salts which stain deep blue in routine preparation of sections has long been designated as "calcification." These cells are actually covered with a deposit of iron salts, which can be demonstrated by the prussian blue method. The test is imperfect when used in tissues fixed by immersion in formaldehyde for long periods, as was the case in this specimen.

become quiescent. The calcification of the blood vessels in the adjacent cerebral tissue is of interest; it represents still another type of process.

This case is important, as it enabled us to determine the characteristics of the process of calcification in a tuberculoma in which there was no question as to the nature of the basic lesion. In so many of the reported cases in which the degenerative changes have completely effaced the typical structure, the question has arisen as to whether one was actually dealing with a tuberculoma. This case serves, then, as a yardstick for further studies.

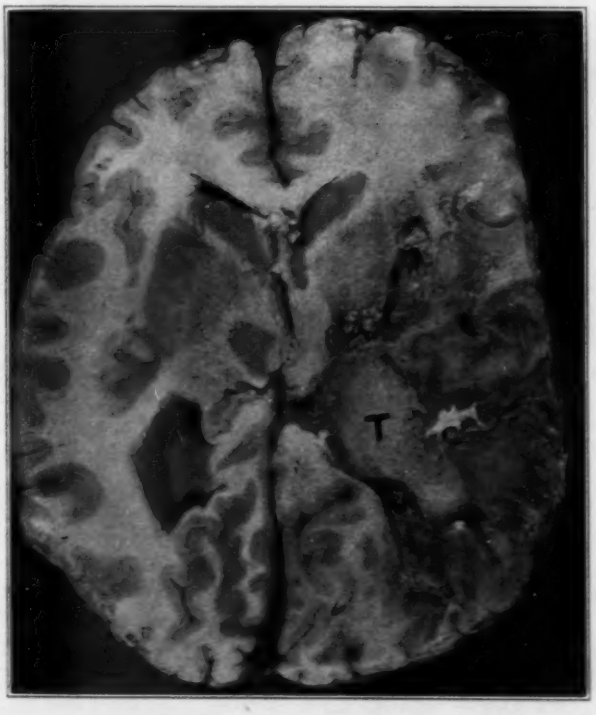

Fig. 2 (case 1).—Horizontal section of the brain, showing the large tuberculoma (*T*) in the white matter of the right parietal lobe. The associated calcareous mass (*c*) appears as an irregular white area lateral to the main part of the tumor. Extensive necrosis of the surrounding brain tissue is evident.

CASE 2.—*Symptoms of acute meningeal irritation in a 3 year old boy; opalescent spinal fluid with formation of pellicle; clinical diagnosis, tuberculous meningitis; recovery; progressive osteomyelitis of left metatarsal bones thought to be tuberculous in origin; persistent drainage from stump of amputation, chronic lesion of rib and mastoid wound; downward course and death eight years after onset, with symptoms of pulmonary disease; autopsy; internal hydrocephalus; calcified tuberculoma beneath right cingulate gyrus; noncalcified tuberculoma in left cerebellar hemisphere.*

A Mexican boy 3 years of age was admitted to the Los Angeles County Hospital in February 1926 with a story of suddenly becoming ill two weeks previously, after exposure to dampness. Pains in the legs and back were followed by generalized convulsions and vomiting of four days' duration. The child had lost his appetite.

On examination, a bilateral internal squint was noted, associated with retraction of the head and bilateral Brudzinski and Kernig signs. Lumbar puncture disclosed opalescent spinal fluid in which a pellicle promptly formed. The fluid was not under increased pressure. There were 525 cells per cubic millimeter, the type of which was not stated. A roentgenogram of the chest was reported as showing no evidence of tuberculosis. The boy was discharged on March 1 with a diagnosis of tuberculous meningitis.

The child was next seen in the clinic on June 17, 1930, with a deformity of the right foot (equinovarus) thought to have resulted from infantile paralysis, which he had contracted three years before. There were two draining ulcers on the dorsum of this foot.

The boy subsequently contracted osteomyelitis of the metatarsal bones of the left foot. Because of its character the lesion was suspected of having a tuberculous origin, although no acid-fast organisms were ever found in the exudate. The left leg was finally amputated in its middle third. The bony lesion proved to be of a tuberculous nature.

A roentgenogram was taken of the chest on July 25, 1931, when the child was brought to the clinic with a chronic papular eruption of the skin. No evidence of pulmonary tuberculosis could be made out.

On Jan. 1, 1932, the boy was readmitted to the hospital with a swelling of two weeks' duration in the right thoracic wall over the seventh rib in the anterior axillary line. A roentgenogram showed alterations in the rib suggestive of osteomyelitis secondary to an abscess in the soft tissues. Resection of the rib was done. Some exudate from the lesion was injected into a guinea pig; subsequently typical tubercles developed in the animal and characteristic acid-fast organisms were recovered. The child was ultimately referred to the Children's Hospital. There was persistent drainage from the recent operative wound, from the stump of the left leg and from sinuses in the region of the sacro-iliac joints.

In October 1933 otitis media on the left developed; this was complicated by mastoiditis followed by generalized convulsions with lateralizing manifestations on the right side. Mastoidectomy was done at the Children's Hospital on October 26.

On March 19, 1934, the boy was readmitted to the County Hospital with a low grade fever and advanced emaciation. There was drainage from the left mastoid wound as well as from the other sites just mentioned. The right knee was swollen and tender. The breath sounds were harsh throughout the chest and were associated with occasional crackling rales at the base of the right lung. The patient died on October 14, at the age of 10½ years, seven years after the onset of his illness.

An autopsy was performed three hours after death by Dr. Eugene Joergensen. Draining sinuses were present in the left mastoid region, in the medial aspect of the supracondylar region of the right arm, in the right anterior axillary line over the seventh and eighth ribs, in the right anterior superior iliac spine, in the lateral aspect of the right knee and in the stump of the left leg.

There were no areas of ulceration or caseation in the lungs. The tracheobronchial glands were enlarged and showed considerable caseation. Exploration of the various draining sinuses showed them to be extensive and complicated and associated with the formation of large abscesses.

A circumscribed caseated area about 2 cm. in diameter was observed in the right parietal bone. The inner table of the skull showed advanced convolutional atrophy. The entire central part of the petrous portion of the left temporal bone was the seat of inflammation. The bone had been eroded through to the dura in several places, although the dura itself had not been penetrated.

The convolutions over the dorsolateral surface of the cerebral hemispheres were moderately flattened. The arachnoid in the region of the basilar cisterns was somewhat opaque, and there seemed to be adhesion of this membrane to the pia in the vicinity of the foramina of Magendie and Luschka. The resulting obstruction evidently accounted for the advanced internal hydrocephalus.

Situated at about the middle of the basilar surface of the left cerebellar hemisphere was a firm nodule about the size of a marble, which proved on section to be a noncalcified tuberculoma.

Section of the brain disclosed marked dilatation of the entire ventricular system and thickening of the ependyma. The septum pellucidum was fenestrated, with irregular openings which permitted direct communication between the lateral ventricles. The interventricular foramina and the cerebral aqueduct were markedly dilated, and the anterior wall and floor of the third ventricle were as thin as tissue paper.

In the subcortical white matter of the medial aspect of the right frontal lobe was an irregular, calcified tumor, the longest diameter of which lay in an anteroposterior direction (3 cm.). Its greatest cross-sectional diameters were 1.3 by 0.7 cm. The nodular mass, which presented a peculiar grayish, semitranslucent appearance, was sharply delineated from the surrounding nerve tissue (fig. 3).

Section through the nodule in the right frontal lobe disclosed an irregular calcareous shell embedded in a hyalinized connective tissue scar. The periphery of the shell was composed of a fusion of many small individual crystals of calcareous salts. No definite evidence of tuberculous granulation tissue remained, except for scattered lymphocytes at the margin of the connective tissue capsule. The surrounding brain tissue showed only a loose glial scar.

Section through the cerebellar tuberculoma revealed the characteristic features of such a lesion.

Comment.—The pains in the extremities and the vomiting which occurred seven years before death were suggestive of meningeal inflammation, and it is likely that the cerebral invasion took place at this time. Hydrocephalus was probably the result of meningeal inflammation and adhesion about the basilar foramina. If the cerebral and the cerebellar tubercle formed at the same time, one may well wonder why one became calcified and the other did not. The histologic features of the cerebellar lesion were characteristic of a tuberculoma, while those of the frontal lesion were not.

CASE 3.—*Epigastric distress, irritability and listlessness in a Mexican boy of 6 years; signs of meningeal irritation; pleocytosis and globulin in spinal fluid; death; tuberculous meningitis; softening of the right corpus striatum with calcified and ossified tuberculoma in external capsule; multiple miliary calcified and ossified nodules in cerebral cortex.*

A Mexican boy aged 6 years was admitted to the Los Angeles County Hospital on July 11, 1935. For three weeks there had been intermittent pain in the upper part of the abdomen with progressive irritability, listlessness and disturbance of

sleep. The past history was essentially negative except for uncomplicated chickenpox two months before admission. A left internal squint had been present since birth. There was no known contact with tuberculosis.

The child was lethargic and appeared to be chronically ill. The skin over the trunk and extremities was dry and scaly. The pupils were regular and equal and reacted sluggishly to light. An old perforation was observed in the left tympanum; the right was perforated with numerous minute openings. The cervical glands were slightly enlarged. The neck was moderately stiff. Impaired resonance over the upper anterior part of the left lung was associated with bronchial breathing. The deep reflexes showed no irregularities. Kernig and Brudzinski signs were elicited.

Lumbar puncture disclosed a clear, colorless fluid under more than 400 mm. of pressure. There were approximately 100 cells per cubic millimeter, consisting of

Fig. 3 (case 2).—Small calcified tuberculoma in the subcortical white matter of the right frontal lobe. The dilated lateral ventricle was the result of chronic thickening of the arachnoid with adhesions to the pia in the cisterna magna and in the cisterna pontis lateralis.

both lymphocytes and polymorphonuclears, the proportions not being stated. Repeated punctures done almost daily disclosed a clear fluid consistently under high pressure and containing between 70 and 80 cells per cubic millimeter, predominantly lymphocytes. It required from 22 to 24 drops of spinal fluid to reduce Benedict's solution. Quantitatively, the sugar varied between 30 and 40 mg. and the chlorides between 610 and 680 mg. per hundred cubic centimeters. Levison's test constantly gave negative results. Wassermann and Kahn tests were negative. There were 16,000 white cells per cubic millimeter of blood, with 92 per cent polymorphonuclears.

A roentgenogram of the chest showed increased density throughout the left hilar and perihilar regions.

Death came on July 19.

An autopsy was performed fourteen and one-half hours post mortem by Dr. P. C. Humphreys. There was no evidence of pulmonary tuberculosis, and while the tracheobronchial lymph nodes were enlarged and darkened, no actual caseation was noticed. An incidental congenital stenosis of the right ureter with consequent hydronephrosis of the right kidney was discovered.

The convolutions of the brain were generally flattened, particularly those of the dorsolateral surface of the right frontal lobe, which seemed larger than its fellow. About the branches of the middle cerebral vessels were seen characteristic miliary nodules. In the basilar cisterns the exudate was so abundant as to obscure the regional structures. On the basilar surface of the right frontal lobe, adjacent to the gyrus rectus, was an irregular area of discoloration and softening.

On coronal section the cerebral tissue was seen to be hyperemic. The lateral ventricles were markedly dilated, the anterior horns showing a deflection toward the left with narrowing on the right. In the genu of the corpus callosum was a small tuberculoma. Section through the softened area on the basilar surface of the right frontal lobe showed the softening to extend into the basal ganglions and external capsule on this side. In the midst of this softened area, in the external capsule, was a small circumscribed calcareous mass, the structure of which suggested a calcified tuberculoma (fig. 4). This mass was situated at a point opposite the outer posterior part of the putamen. On closer study the mass was seen to be made up of several distinct areas of calcification. It measured 1 by 0.5 cm. in its greatest diameters.

Further sections of the brain showed a number of other small calcified nodules, two in the cortex of the left parietal lobe and two in that of the left frontal lobe. The nodules varied from 2 to 6 mm. in diameter. As in the case of the first mass, they were made up of two or three separate masses which had become fused.

Microscopically, the typical characteristics of tuberculous meningitis were in evidence. Sections through the various calcareous masses disclosed an irregular calcified shell enclosed within a hyalinized connective tissue capsule, which corresponded closely in structure to that observed in the 2 cases just cited. In addition, osteoid tissue in the process of formation was noted in portions of this shell. Apparently, either the irregular calcareous masses were deposited within this osteoid tissue or the osteoid tissue had developed around the deposits. The newformed bone was not evenly calcified, as is normal bone.

In the hyalinized scar elongated, smooth-margined slits suggested the recent presence of cholesterol crystals.

The only possible evidence of an inflammatory process was the presence of thinly scattered lymphocytes at the margin of the connective tissue capsule.

The small blood vessels in the nerve tissue at the margin of the mass were the seat of irregular, laminated calcospherites.

Comment.—This case is of special interest because, as in case 2, there were in the brain both calcified and noncalcified lesions. Again the question arises: Are these lesions of the same age? If so, why did one type of lesion undergo calcification and ossification while the other did not? We have found no answer to this question.

Perhaps of even greater interest is the occurrence of actual bony formation in the large tumor as well as in the miliary nodules. This adds another instance to the list of intracranial lesions in which formation of bone may take place.

THE SIGNIFICANCE OF CALCIFICATION AND OSSIFICATION IN TUBERCULOMA OF THE BRAIN

Deposition of calcium salts and, less commonly, formation of true bone are consequences of healing in tubercles, regardless of their location. These processes occur typically in the lymph nodes along the respiratory passages and in tubercles of the lung. Because of the more

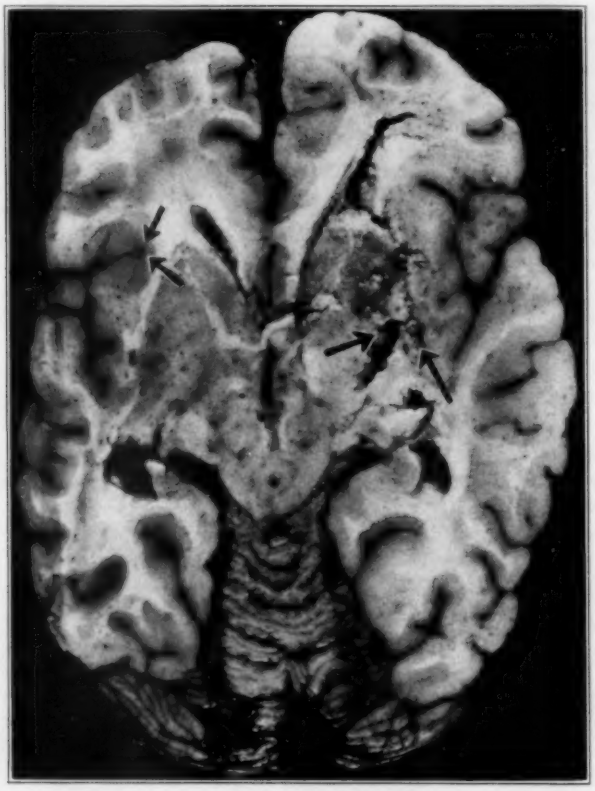

Fig. 4 (case 3).—Horizontal section of the brain, showing extensive softening of the right basal ganglia and centrum of the right frontal lobe and external capsule. A small calcified tuberculoma was observed (arrows) in this area. On the left side were seen several small calcified and ossified tubercles (arrows) in the leptomeninges.

malignant character of tuberculous inflammation in the meninges and brain, healing of tubercles in these structures in much less common, and calcification and ossification would therefore be observed less frequently. As has been repeatedly emphasized, healing of a tubercle in the brain or elsewhere is not absolute evidence of complete quiescence. "Healed"

tubercles in the meninges [23] or calcified tuberculomas within the brain tissue may be the source of fatal tuberculous meningitis.

As has been shown in the foregoing discussion of cases previously reported and of those which we personally studied, regressive changes in tuberculomas of the brain may be followed by deposit of calcium or by formation of bone. To be sure, the distinction between the two processes has not always been clearly drawn, particularly in the earlier reports, in which critical histologic studies were not always made. It is obvious that calcification is more common than ossification and probably precedes it. In Siemon's case ossification as well as calcification was observed in a tuberculoma of the frontal lobe. In one of our cases (case 3) the same condition was seen in multiple tuberculomas of the cerebral hemispheres.

CHARACTERISTICS OF CALCIFICATION AND FORMATION OF BONE

The deposit of calcium as a consequence of a tuberculoma may occur in any one of several situations. It may be noted in the walls of blood vessels of the brain at the margin of a tuberculoma. It may similarly be observed in the walls of vessels in the central portion of a partially degenerated tuberculoma. More commonly it occurs in the form of a shell within the necrotic center of a tuberculoma.

Calcification in the walls of blood vessels at the margin of a tuberculoma is not characteristic of this lesion. It has been observed at the margins of gliomas and even of the more malignant glioblastomas.[24] Calcareous salts are deposited in the form of isolated round or oval globules, which tend to coalesce and to outline the blood vessels in the neural tissues (fig. 5). The process is believed to be due to a local disturbance of tissue respiration. The soluble calcium salts are thought to unite with an excess of carbon dioxide to form the insoluble calcium carbonate which is deposited in the walls of the smaller blood vessels.

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23. The matter of a cure in cases of tuberculous meningitis has always been a subject of much interest. That healing can occur in each case has been proved beyond a doubt, as has been indicated by the studies of A. E. Martin (The Occurrence of Remissions and Recovery in Tuberculous Meningitis, Brain **32**:209, 1909) and A. Cramer and K. Bickel (La méningite tuberculeuse est-elle curable? Ann. de méd. **12**:226, 1922). As far as we can learn, there have been no reported cases of calcification in healed meningeal tubercles. In one of the cases reported here (case 3) and in another case of healed tuberculous meningitis, to be reported elsewhere (Courville, C. B., and Evans, H. S.: Residual Lesions in Healed Tuberculous Meningitis, Bull. Los Angeles Neurol. Soc. **2**:125, 1937), calcified and ossified meningeal tubercles were discovered at autopsy.

24. Courville, C. B., and Adelstein, L. J.: Intracranial Calcification with Particular Reference to That Occurring in the Gliomas, Arch. Surg. **21**:801 (Nov.) 1930.

The second type of calcification is similar to the one just described, in that calcium is deposited in blood vessels within the tuberculoma (fig. 6). The vessels are quite clearly shown in the histologic preparation, which suggests that complete necrosis has not taken place. The presence of the calcium is probably to be accounted for in a similar way.

In the third type, which is the common and characteristic one, calcification follows more marked regressive changes in the lesion. In fact, identifying remains of the tuberculoma are usually not observed, and it has often been difficult or impossible to identify the lesion. We

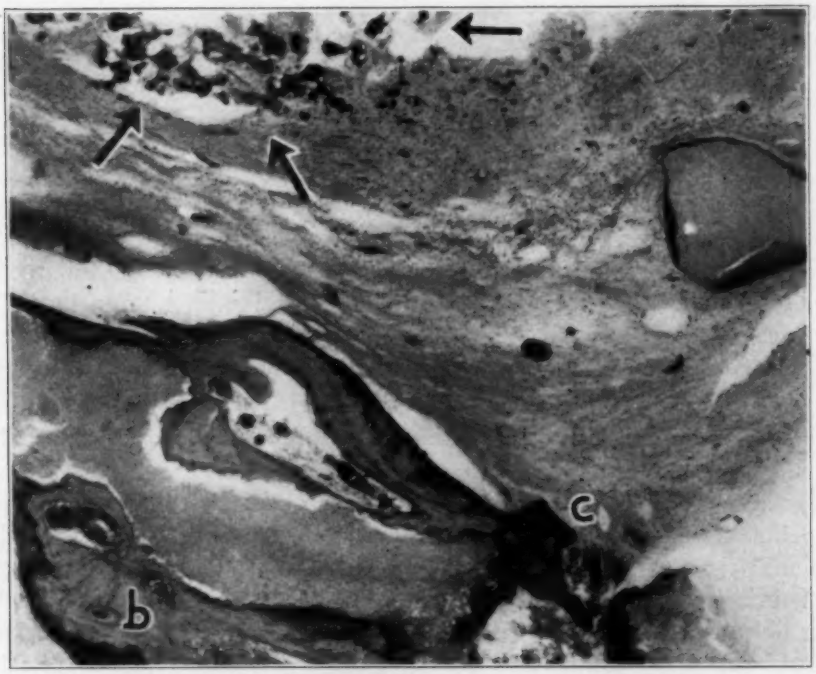

Fig. 5 (case 3).—Calcification of blood vessels (arrows) in the brain tissue at the margin of the tuberculoma, in which both calcification (*c*) and formation of bone (*b*) have occurred. Hematoxylin and eosin stain; × 45.

shall show, however, that the process of calcification and ossification is characteristic of the lesion and that one can be assured of the original nature of the lesion on this basis. In our cases this conclusion is made certain, for in case 1 calcification occurred only in the central portion of an unusually large tuberculoma, and in cases 2 and 3 the association of calcified and typical noncalcified lesions made the situation obvious.

The lesion consists of three well defined zones or areas: (1) an outer zone of hyalinized connective tissue, (2) a more or less irregular calcareous shell and (3) a structureless necrotic core. The outer layer

or zone of hyalinized connective tissue may contain some residual cellular elements indicative of a tubercle (round cells, plasma cells, fibroblasts and new-formed blood vessels), but these are often entirely absent. This layer, which has been designated by other writers as the capsule, is usually sharply delineated from the enveloping neural tissue. The zone is not of uniform width. Owing to the collapse and fragmentation of the calcareous shell, it may be wide in some regions and narrow in others.

The calcareous shell, which in this connection is of particular interest, is composed of myriads of small calcospherites which become confluent

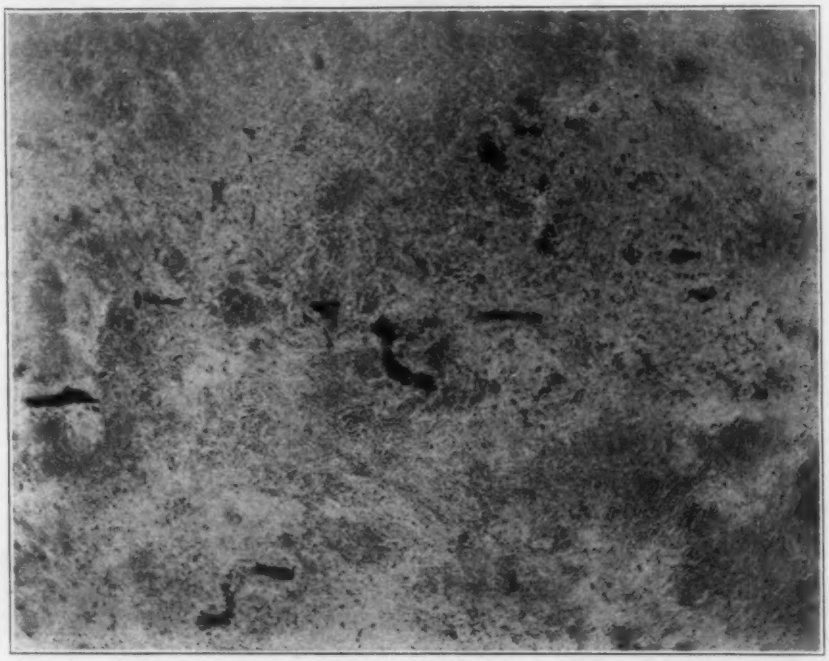

Fig. 6 (case 1).—Calcareous salts deposited in blood vessels in an incompletely necrotized portion of the large cerebral tuberculoma. This process occurred a short distance from the heavily calcified shell shown in figure 7. Hematoxylin and eosin stain; × 95.

to form a band, often of considerable width (fig. 7). These individual globules, seen best in the looser outer portion of the zone, are small, discrete, round or slightly oval masses with a dark periphery and a lighter center. The shell is usually collapsed and fragmented, not forming a perfect or complete sphere. It is likewise not of uniform thickness.

The central, structureless core probably represents the remains of the central, necrotic portion of the tubercle. It is made up of small pale granules. The gradual absorption of this material, with contraction of

the connective tissue capsule, probably explains the collapse and fracture of the calcareous shell.

It is of importance in this connection to learn whether calcification in tubercles is identical regardless of the type of tissue in which the lesion is situated. A survey of the literature on the characteristics of calcification in tuberculomas has largely been fruitless. Scattered remarks in textbooks indicate the calcification to be central,[25] as is the case in experimental tubercles.[26] Actual study of a calcified tubercle in a

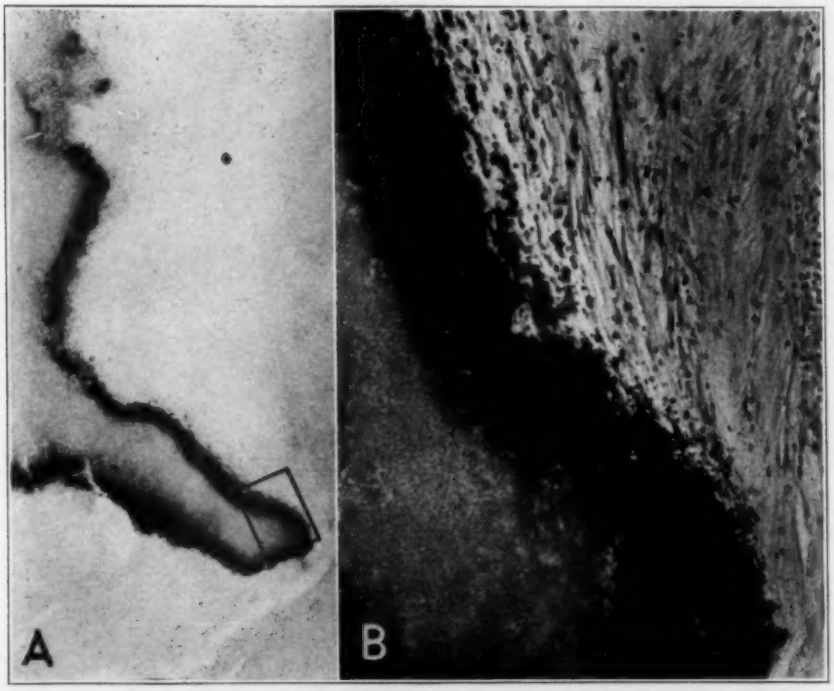

Fig. 7 (case 1).—Calcareous shell in tuberculoma of the brain. *A* shows a portion of the irregular, contracted shell with a structureless, necrotic center; × 30. *B* shows an enlarged portion of the shell, which is composed of myriads of crystals of calcium salts; × 145. Hematoxylin and eosin stain.

mediastinal lymph node showed a calcareous shell, although the central core was small. This suggests that the process is essentially the same,

25. Delafield, F., and Prudden, T. M.: A Text-Book of Pathology, ed. 15, revised by Frances Carter Wood, Baltimore, William Wood & Company, 1931, p. 717.

26. Spies, T. D.: The Calcification of Tubercles by Means of Irradiated Ergosterol, Am. J. Path. **6**:337, 1930; The Calcification of Tubercles by Means of Irradiated Ergosterol in Experimental Chronic Tuberculosis, Am. Rev. Tuberc. **23**:169, 1931.

although the central core may be greater or less in extent, depending somewhat on the type of tissue in which the tubercle is located (or on the blood supply of the tissue).

Formation of bone is a less common and probably a secondary process. In some lesions new-formed bone is observed in some portions of the calcareous shell. It has never been known to form a complete bony shell, although theoretically such an eventuality is possible. In some cases the bone assumes the appearance of the adult type by deposit of calcium in the osteoid tissue.

POSSIBLE MECHANISM OF CALCIFICATION AND OSSIFICATION

The possible reasons for the deposit of calcium in these healed tuberculomas merit consideration. It has been found that calcium tends to be deposited in lesions containing or composed of completely dead tissue which for any reason is not absorbed.[27] A long-existent tuberculoma in any location presents a classic example of such a situation. The extensive central necrosis or caseation represents tissue which is completely dead and which, because of the poor circulation, is not absorbed. Just what intimate situations exist which favor the deposit of calcium salts is not entirely clear, but it is likely that there is precipitation of calcareous salts in the exterior portion of the tubercle, where the circulation is still not entirely obliterated. The impaired tissue respiration probably favors the union of carbon dioxide and the soluble calcium salts in the blood to form insoluble calcium carbonate.

The occurrence of calcium in tubercles has also been explained on the theory that fatty acids attract calcium and, by combining with it, form calcium soaps, which unite with soluble phosphates and carbonates to form insoluble calcium phosphates and carbonates.[28]

Still another factor should be considered. In healed tuberculomas there is gradual replacement of the necrosed tissue by connective tissue, which contracts to form a fibrous scar. This is strongly suggested by the presence of connective tissue, which forms the remainder of these healed lesions. This connective tissue evidently undergoes more or less complete hyalinization, as is again suggested by the absence of structure in the scar immediately about the calcareous mass. This process of hyalinization is also said to favor the deposit of calcium. Whether the calcium is actually deposited in the necrotic tissue near the periphery of a tubercle or whether replacement with connective tissue and hyalinization precede the process is not evident.

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27. Wells, H. G.: Chemical Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1925, p. 489.

28. Karsner, H.: Human Pathology, ed. 3, Philadelphia, J. B. Lippincott Company, 1931, p. 96.

From this purely morphologic study, the relative importance of these three factors—impaired tissue respiration, formation of fatty acids and hyalinization of connective tissue—in the process of calcification cannot be determined. One can only state that the process begins in a zone just within the external margin of the tuberculoma, probably at the juncture of the central necrotic area and the peripheral border of granulation tissue. Thus is formed a calcareous shell, which ultimately becomes irregular and broken as the connective tissue at the border contracts and the necrotic material in the center is slowly absorbed.

This explanation, however, does not suffice for the occasional calcification of small vessels in the central necrotic regions. In such cases necrosis with occlusion of blood vessels is apparently not complete, and the theory of disturbed tissue respiration would apply more particularly.

The formation of bone within a tuberculoma is evidently much less common, if the facts gathered from a survey of the literature and from our own experience are of any significance. For example, we found in the report of Siemon the only definite statement that bony formation was present in a tuberculoma. It occurred in a tuberculoma in but 1 of our cases, but in this case it occurred also in a number of miliary tubercles which had also undergone the process of calcification. The bone which is present is characteristic of new-formed osteoid tissue in which calcium has not yet been deposited (fig. 8). A study of the details in our case is of interest. Either the bone developed within the area in which calcium had been deposited, or calcium was laid down in the new-formed bone in the same way as it was in the hyalinized connective tissue, namely, in the form of conglomerations of calcareous crystals (fig. 9). The appearance of the lesions lends strength to the conception of Nicholson [29] that the presence of calcareous salts in an abnormal situation tends to stimulate the connective tissue cells in this region to undergo a metaplasia into bone cells.[30]

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29. Nicholson, G. W.: The Formation of Bone in a Calcified Epithelioma of the Skin, J. Path. & Bact. **21**:287, 1916-1917.

30. This brings up the interesting problem as to the actual mechanism of bone formation in abnormal situations. Our observation again seems to bear out the theory of R. Leriche and A. Policard (The Normal and Pathological Physiology of Bone, St. Louis, C. V. Mosby Company, 1928) that bony formation is not the secretory product of a specific cell but is rather the result of a transformation of connective tissue cells to osteoblasts and that the resulting osteoid tissue is transformed into true bone by a subsequent deposit of calcium. This is evidently an entirely different process than that occurring, for example, in a case of metastatic osteogenic sarcoma of the brain, in which formation of bone was evidence of a specific cellular tendency to perform this function (Harding, W. G., and Courville, C. B.: Bone Formation in Metastases of Osteogenic Sarcoma: Report of Case with Metastases to the Brain, Am. J. Cancer **21**:787, 1934).

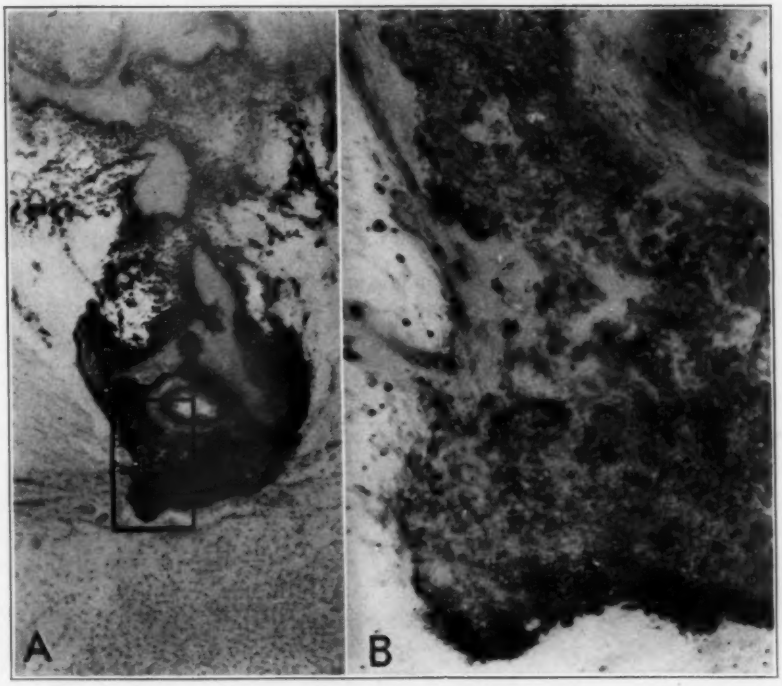

Fig. 8 (case 2).—Osteoid tissue forming in a calcareous shell in a small tuberculoma of the brain. *A* shows a portion of the calcareous shell; × 30. *B*, enlargement, shows newly-formed osteoid tissue in the calcareous shell; × 160. Hematoxylin and eosin stain.

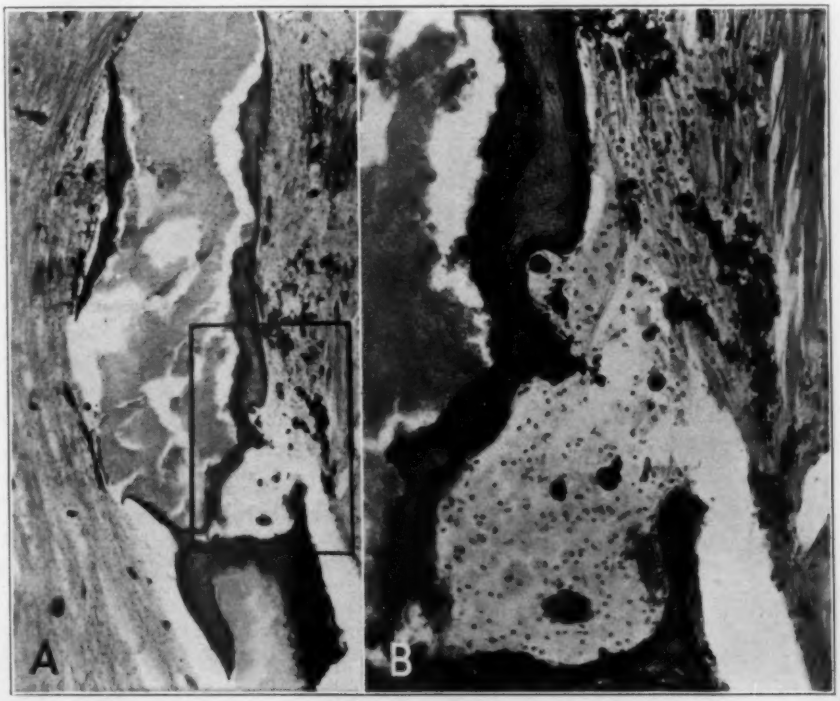

Fig. 9 (case 3).—Capsule enclosing a calcareous and osseous shell of a cerebral tuberculoma. *A* shows the collapsed shell with its necrotic center; slightly reduced from × 45. *B* shows a portion of the capsule with deposits of calcareous salts and bony formation in the adjacent shell; slightly reduced from × 135. Hematoxylin and eosin stain.

Formation of bone seems to take place deep within the calcareous shell, where in turn an irregular and usually incomplete bony shell may occur. At times only small areas of the shell may become ossified (fig. 10).

From our observations one would conclude that the formation of new bone is a later process, occurring some time after calcium has been deposited. In fact, it is probably encouraged by the presence of calcareous salts, which tend to stimulate the metaplasia of connective tissue cells into osteoblasts. The reported cases are too few and the details

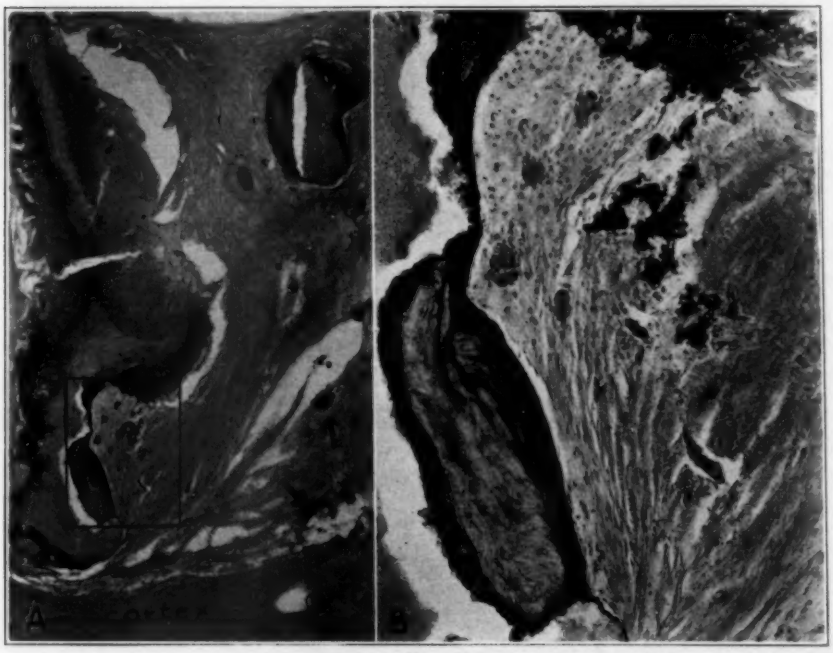

Fig. 10 (case 3).—Formation of bone in a conglomerate meningeal tubercle. *A* shows two separate calcareous shells with capsules, the larger of which has collapsed. Calcium has also been deposited in the regional blood vessels (arrows); × 24. *B* shows the detail of the bony formation, which is assuming adult type with deposit of calcium. Calcareous salts in the shell (upper right) and in the capsule (right) are also shown; × 96. Hematoxylin and eosin stain.

too obscure for one to draw any conclusions as to the length of time required for this process.

SUMMARY AND CONCLUSIONS

1. The occurrence of calcification or ossification in tubercles of the brain, evidently indicative of partial or complete healing of these lesions,

is relatively rare. We have collected a series of 15 cases from the literature and have added 3 which came under our observation.

2. Calcification or ossification occurs in about 7 per cent of the cases of tuberculoma of the brain.

3. The process of calcification or ossification may occur in miliary meningeal tubercles ("healed tuberculous meningitis") as well as in gross tuberculomas. It does not necessarily occur in all tubercles or tuberculomas present in the brain in a given case.

4. The process of calcification is preceded or accompanied by a transformation of the peripheral zone of granulation tissue into a zone of connective tissue, which becomes more or less completely hyalinized, presumably owing to impairment of its circulation incident to its contraction.

5. Calcium is deposited in the periphery of the central necrotic area and beneath the connective tissue capsule to form a calcareous shell. Whether calcium is deposited in the dead tissue before or after fibrosis and hyalinization occur is unknown, since the intermediate stages have not as yet been studied. The shell assumes an irregular contour and is often broken, probably as a result of contracture of the connective tissue capsule and gradual absorption of the underlying necrotic material. We believe that this irregular, broken calcareous shell is characteristic of the deposit of calcium in tubercles and that it does not occur in any other intracranial lesion with which we are familiar.

6. The actual mechanism of calcium deposition is uncertain. It may be the result of impaired tissue respiration, it may be due to the presence of fatty acids in the decadent tissues, or it may possibly be favored by hyalinization of the adjacent connective tissue capsule. Since it is deposited in the form of a shell beneath the external connective tissue layer, accessibility to the circulation seems to be necessary, possibly because the blood is the source of calcium.

7. The process of formation of bone is less common, and in the 2 cases available for study (case of Siemon and our case 3) in which this occurred calcification as well as bony formation was present. This suggests that the presence of calcium favors formation of bone, according to the conception of Nicholson. Possibly some unknown stimulating effect of the calcium on the connective tissue favors metaplasia of connective tissue cells into osteoblasts.

CALCIFICATION ABOUT THE FLEXOR CARPI ULNARIS TENDON

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During the past year or so we have had an opportunity of studying a number of patients, all of whom presented such strikingly similar symptoms as to warrant their being grouped together as having a definite clinical entity. Typically, there were sharply localized pain and tenderness over the area around the pisiform bone; a pathognomonic limitation of motion at the wrist; occasional signs suggesting an inflammatory reaction; a characteristic roentgenogram, and early subsidence of symptoms. When we referred to the literature for some help in understanding the condition, we were afforded scant assistance. Except for a single case reported by Cohen [1] and the casual statement of Codman [2] that he knew "of one case in the flexor carpi ulnaris," no mention could be found of the condition, either in the clinical or in the roentgenologic literature. Neither Codman nor Cohen presented any histologic evidence to justify their belief that the site of the lesion was the tendon itself. We are inclined to share the opinion of Codman and Cohen, but we can offer no positive proof and the present consideration is undertaken from clinical rather than from pathologic interest.

Though all of our cases showed a basic similarity, there seemed to be sufficient variation to justify subdivision of the conditions into three main types similar to those suggested for injuries to the supraspinatus tendon: (1) a hyperacute form, (2) an acute form with calcification and (3) an acute form without calcification.

THE HYPERACUTE FORM

REPORT OF CASE

CASE 1.—H. H. G., a 29 year old man, was admitted to the hospital on Dec. 9, 1935, complaining that two days before he had noted a dull pain in the left wrist while making a plaster of paris splint. During the day the pain became more

From the service of Dr. Harry Finkelstein at the Hospital for Joint Diseases.

1. Cohen, I.: Am. J. Surg. **38**:172, 1924.

2. Codman, E. A.: Boston M. & S. J. **154**:613, 1906; The Shoulder, Boston, The Author, 1934, pp. 68-83.

severe, and all motion of the wrist became so painful and so restricted that an anterior splint was applied to immobilize the wrist. Despite this rest and the exhibition of large amounts of salicylates, sleep was impossible because of the throbbing pain on the ulnar side of the volar aspect of the left wrist. Early the following evening the patient had a mild chill and a feeling of malaise and anorexia. The temperature was 102 F. The hand and wrist were held in neutral position and there was an area of redness and swelling directly over the left pisiform bone. Extending upward as far as the middle of the upper arm, there were several red streaks, suggesting lymphangitis. There was marked tenderness over the swollen area, but no evidence of fluctuation. Any attempt at normal

Fig. 1 (case 1).—Anteroposterior view, showing an irregular, snowshoe-like shadow of varying density over the upper end of the pisiform bone. On a later roentenogram this shadow assumed a more sausage-like shape, and still later it disappeared completely.

extension or radial deviation of the wrist caused exquisite pain in the swollen area. There was no evidence of motor or sensory disturbance in the hand and no enlargement of the epitrochlear or axillary glands. The symptoms did not subside, and the patient was sent to the hospital, where the clinical findings were essentially the same. The temperature remained at about 100 F.; the pulse rate was somewhat over 100 and the impression was obtained that the patient was suffering from lymphangitis.

A roentgenogram (fig. 1) made after his admission to the hospital revealed several irregular densities in the soft tissues, on the inner aspect of the wrist and between the styloid process of the ulna and the pisiform bone. These densities suggested osteitis of an accessory bony nucleus, or osteochondritis of the pisiform

bone. The swollen area was aspirated in an effort to determine the presence of pus, but none was obtained.

During the forty-eight hours following his admission to the hospital the patient was given hot hand baths, and the pain gradually subsided. At this time a roentgenogram revealed that there was a distinct diminution in the density of the previously mentioned small body below the ulnar styloid process. Irregular calcification was distributed longitudinally from a point immediately below the styloid process of the ulna, downward into the soft tissues and externally to the pisiform bone, for about 1 inch (2.5 cm.). The neighboring bones showed no specific alteration. Roentgenographically, the appearance was extremely unusual, and not

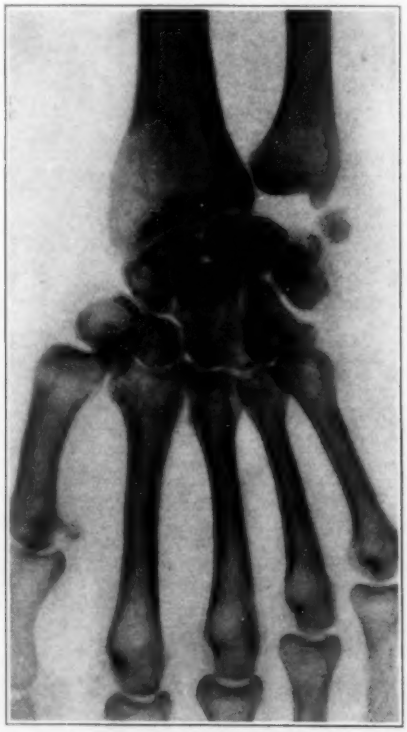

Fig. 2 (case 2).—The shadow in this case is circular, as if it were enclosed in a limiting membrane, such as a bursa.

characteristic of any pathologic process. The roentgenogram suggested calcification in the ligamentous structures of the part. On the fifth day pain had completely disappeared. A roentgenogram subsequently taken for check-up purposes revealed complete disappearance of any densities, and all irregularities in the wrist had completely disappeared. (An almost identical process subsequently developed at the insertion of the triceps.)

THE ACUTE FORM WITH CALCIFICATION

Case 2.—M. P., a 50 year old woman, was first seen in the outpatient department on Nov. 9, 1936. There was a history of pain, redness and swelling over

the ulnar aspect of the left wrist for about one week. No history of any direct blow or recent acute illness could be elicited. Examination disclosed redness, swelling and pseudofluctuation over the ulnar half of the volar aspect of the left wrist. Extending upward along the ulnar border of the forearm there was a moderate induration. There was marked tenderness on pressure over the pisiform bone, with marked pain on radial or dorsal deviation of the hand. Clinically, the condition resembled acute tenosynovitis or osteomyelitis of the lower end of the ulna. A roentgenogram (fig. 2) revealed a calcific deposit between the styloid process of the ulna and the pisiform bone. The diagnosis was thereupon clarified,

Fig. 3 (case 3).—Lateral view. The shadow in this case is lacelike, suggesting a Medusa head, and seems to arise directly from the periosteum of the pisiform bone.

and the patient's wrist was strapped and physical therapy advised. The patient was given short wave therapy for one or two treatments. On her return to the outpatient department for one follow-up examination, the symptoms had completely subsided. Since that time she has not returned for examination.

CASE 3.—S. G., a 38 year old man, was first seen on Oct. 27, 1936. A cellist by profession, the patient stated that he first noted pain in his left wrist six or eight months before, when he struck the volar aspect of his left wrist against the belly of the cello while advancing into the higher positions. In spite of inter-

mittent pain which occurred only on exertion, the patient received no treatment and continued at his work. Two days before his admission to the hospital the pain suddenly became excruciatingly severe, and the patient was forced to discontinue playing the cello. Examination revealed marked tenderness over the left pisiform bone, directly at the insertion of the flexor carpi ulnaris. There was moderate swelling, but no inflammation and no redness. Dorsal and radial deviation caused extreme pain. A roentgenogram (fig. 3) showed a hazy, serpentine calcification, which suggested periostitis, and a destructive process in the pisiform bone. Experience had, however, taught us to discount this roentgen picture. The

Fig. 4 (case 4).—The irregular, oval shadow is located nearer the tip of the ulna than in the other cases.

patient's hand was strapped, and he was given several applications of short wave therapy and a mild analgesic. Within three days the symptoms had completely disappeared, and the patient was able to resume his usual activities.

Case 4.—The patient was a private patient of Dr. Harry Sonnenschein, who gave us permission to reproduce the roentgenogram. The details of the case are not available, but it is reported that several months after a fracture of the elbow the patient suddenly began to complain of severe pain in the wrist. A roentgenogram (fig. 4) showed the typical calcification. The wrist was immobilized, and within three or four days the symptoms of pain, swelling and limitation of motion had vanished completely.

ACUTE FORM WITHOUT CALCIFICATION

CASE 5.—R. G., a 37 year old woman, was first seen in May 1935, with a history of sudden pain over the left pisiform bone. She believed that she might have struck herself while at her housework. No history of recent illness was obtained. Moderate swelling, redness and marked tenderness on pressure over the pisiform bone were noted. There was marked pain on radial and dorsal deviation of the hand.

A roentgenogram taken at this time was reported as being "negative." There was, however, a peculiar triangular shadow in the greater multiangular bone, suggesting fracture or embryonal fissure. The wrist was strapped, and the patient was given physical therapy. After several treatments the symptoms completely subsided. In March 1936, after a blow against the lower surface of her right forearm, the patient complained of pain in the right wrist. Examination three days after the alleged injury showed definite swelling over the pisiform bone, with slight redness and elevation of the local temperature. The area was exquisitely tender to the touch. No fluid could be felt in the area. There was marked accentuation of pain on passive extension of the wrist and on active flexion against resistance. The patient was advised to have a roentgenogram taken, but she refused, since the symptoms began to subside immediately after the first short wave treatment. Within several days the symptoms completely disappeared, and the patient has been well ever since.

CASE 6.—P. D., a 38 year old man, was first seen on July 29, 1936, complaining of pain of one week's duration on the volar aspect of the right wrist. There was no history of any definite blow or acute illness. Examination disclosed swelling over the proximal row of carpal bones on the ulnar side of the right forearm. There were no signs of local inflammation. There was marked tenderness on pressure just over the pisiform bone, at the insertion of the flexor carpi ulnaris tendon. The patient was advised to have a roentgenogram taken, but he did not return for a follow-up examination.

The following two cases were observed in the practice of Dr. Daniel Levinthal, of Chicago, who has given us permission to report them.

CASE 7.—F. L., a 40 year old man, an executive, was seen on March 26, 1935. He complained of pain, swelling and limitation of motion of the left wrist of fifteen days' duration. No other joints were involved, and there was no history of injury.

Examination revealed swelling over the volar aspect of the left wrist, with palpable thickening and tenderness of the flexor carpi ulnaris tendon. Extension of the wrist was painful. There was no obvious focal infection, although the tonsils had not been removed and roentgen examination of the teeth had not been made recently.

Roentgenograms failed to reveal any pathologic appearance of the bones, but in the second film the roentgenologist noted fluid in the course of the flexor carpi ulnaris tendon.

Treatment consisted of application of a dorsal splint which maintained the wrist in flexion, and gentle physical therapy. Improvement began promptly and was steady. The patient was last seen on April 9, 1935, at which time he was almost, if not completely, free from symptoms.

CASE 8.—M. M., a 32 year old broker, was seen on Nov. 18, 1936. He complained of pain and swelling of the right wrist of twenty-four hours' duration,

with radiation of the discomfort up the forearm. The onset had been sudden, and there had been no injury. No other joints were involved.

Examination revealed redness, tenderness and swelling along the course of the lower end of the right flexor carpi ulnaris tendon. Pain was elicited on extension, and relief was obtained by flexion of the wrist.

Treatment consisted of application of a dorsal plaster splint, with the wrist in moderate flexion, and gentle radiant heat. The patient was last seen one week later, on Nov. 25, 1936, and he was completely relieved except for slight tenderness, which we later heard disappeared in a short time.

COMMENT

Though we have reported a relatively insignificant number of cases, we believe the condition described is more common than has been realized. It is hoped that the future will disclose many additional instances of the disability. Because the affliction has been of such short duration and has responded readily to conservative therapy, we have not felt justified in removing pathologic material. However, we are hopeful that this defect in our presentation may be remedied shortly. In the absence of any pathologic specimen we have been forced to infer the location of the calcium deposition. Anatomically considered, the site of the pathologic process may be: (1) the occasional bursa subadjacent to the flexor carpi ulnaris, (2) the peritendinous soft tissues, (3) the tendon itself. From a clinical point of view, the syndrome here presented resembles in many respects that described for the supraspinatus tendon by Codman, Brickner,[3] Moschcowitz[4] and others. It resembles also a similar condition found in the gluteus medius muscle, which has more recently been described by Goldenberg and Leventhal.[5] Though it is known that in both the supraspinatus and the gluteus medius tendon the biologic process probably consists of calcification and later ossification in an area of necrosis in a tendon, the former condition is still erroneously referred to as subacromial or subdeltoid bursitis, while the latter is described as peritrochanteric bursitis or as calcareous gluteal bursitis. The same possibility for misapprehending the location of the calcification presents itself with the flexor carpi ulnaris tendon as with the other two tendons just mentioned, for an occasional bursa is to be found between the tendon and the volar aspect of the pisiform bone, which forms part of its insertion. This bursa appears to have been first described by Monro,[6] who stated that there is a very small bursa between the tendon of the flexor carpi ulnaris and the os pisiforme.

3. Brickner, W.: Am. J. Surg. **30**:108, 1916; Am. J. M. Sc. **149**:351, 1915.

4. Moschcowitz, E.: Am. J. M. Sc. **150**:115, 1915.

5. Goldenberg, R. R., and Leventhal, G. S.: J. Bone & Joint Surg. **18**:205, 1936.

6. Monro, A.: Outline of the Anatomy of the Human Body in Its Sound and Diseased State, Edinburgh, A. Constable & Co., 1813, vol. 1, p. 471.

Other anatomists either have made no mention of the bursa or have dismissed it with passing reference to its occasional presence. Gruber has been cited as having made a special study of this bursa, but his report was not accessible for reference. Apart from the fact that calcification within a bursa does not occur, the size of the bursa as compared with the varying appearance of the shadow in the same person would preclude the belief that the bursa was the site of the deposition of calcium.

On the other hand, the anatomic disposition of the tendon readily explains the variations in the shadow seen in the roentgenograms. Frohse [8] gave an excellent description of the insertion of the flexor carpi ulnaris tendon. He considered the pisiform bone as a sesamoid, situated in the tendon. Before its insertion into the pisiform bone, the tendon gives off two slips: a volar slip, described by Henle,[9] which makes up the ligamentum carpi volare, and a dorsal slip, which winds around to the dorsum and is inserted into the ligamentum carpi dorsalis. After its insertion into the pisiform bone, the tendon is continued downward and medially, as the pisohamate ligament, which terminates in the ligamentum basum volare. It is probable that the shape and size of the calcification depend in large degree on the location and extent of the deposition of calcium in the tendon or the peritendinous tissues.

The possibility that the calcification may be located in the peritendinous tissues has already been noted by Finkelstein.[10] It is well demonstrated in the following case, in which the calcification was seen on the radial side of the volar aspect of the wrist. The details of this case were supplied by our mentor, Prof. Arthur Steindler.

CASE 9.—H. D., a 32 year old white woman, a physician, was first seen Nov. 20, 1936. In April the patient had noted pain on the volar surface of the wrist at the base of the greater multiangular bone. She said motion and work made it ache. On immobilization, discomfort subsided. The pain had gradually become worse, and the wrist was tender to pressure. One month previous to the patient's first visit a lump was noted, and of late her wrist had been aching constantly. At times, in the evenings, she noted that her wrist was swollen, causing much discomfort.

On examination a tender lump was noted. The laboratory tests which were performed showed no abnormality. The roentgenogram (fig. 5) showed a small round radio-opacity on the volar aspect of the hand. Some question was raised as to whether this shadow might not represent an accessory ossicle. This opinion

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7. Footnote deleted by author.

8. Frohse, Fritz, and Frankel, Max, in von Bardeleben, K.: Handbuch der Anatomie des Menschen, Jena, Gustav Fischer, 1908, vol. 2, pt. 2, p. 122.

9. Henle, J.: Handbuch der systematischen Anatomie des Menschen, Braunschweig, F. Vieweg u. Sohn, 1871, vol. 1, pt. 3, p. 206.

10. Finkelstein, H.: J. Bone & Joint Surg. **12**:509, 1930.

was, however, finally dismissed, and the patient was operated on under general anesthesia on Nov. 21, 1936, with the provisional diagnosis of tumor of the left wrist.

An incision was made over the volar aspect of the wrist, extending slightly over the thenar eminence, apparently in the region of the flexor carpi radialis tendon. This tendon was cut down on, and a very definite lime salt incrustation

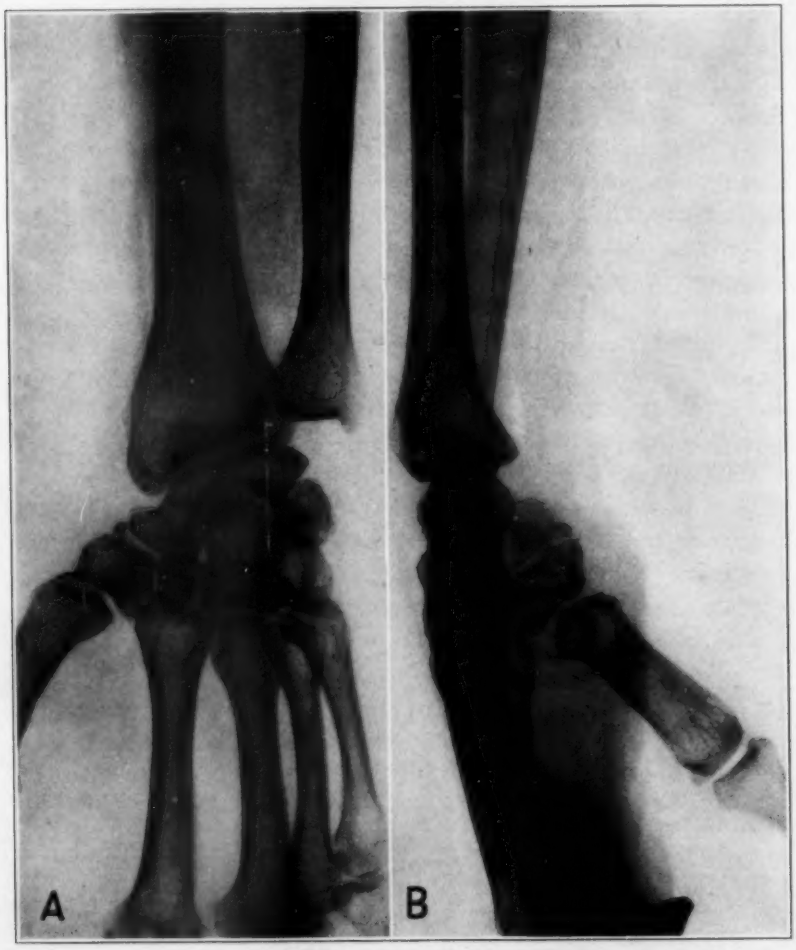

Fig. 5 (case 9).—*A*, anteroposterior view, showing a small, oval, calcific shadow between the greater multiangular and the navicular bone. *B*, lateral view, showing the volar position of the radio-opacity, which at operation was found to be a calcification in the sheath of the tendon.

was found within the substance of its sheath. The incrustation was removed in toto and the wound closed in layers. Because of the small size of the incision, there appears to have been some doubts as to the exact tendon about which the calcification was found. This is, of course, immaterial. The important point is, as Dr. Steindler assured us in another letter, under date of March 3, 1937, that

"the calcium deposition was in the sheath of the tendon." He stated: "After removal of the mass the tendon was seen to be smooth and grossly uninvolved in the pathologic process. The site of the involvement was not at the origin or the insertion of the tendon. Preoperatively, there was little or no impairment of the action of the tendon. The calcium deposition was palpable beneath the skin as a small mass and was tender. The patient at this date still experiences complete relief."

Roentgenographically, this case resembles those which we have presented. Yet the duration of the symptoms and the absence of typical limitation of motion raise the question as to whether a fundamental difference may not exist in spite of the superficial resemblance. That calcification does occur in tendons or muscles is sufficient justification for the belief that it may have occurred there in these cases. Obviously, however, final pathologic designation of the clinical condition must be deferred until further microscopic studies have clarified the issue.

No definite etiologic factor can be established. Case 1 certainly seems to suggest an infectious origin. On the other hand, in the case reported by Cohen and in our cases 3 and 5 the symptoms are so definite that the relation of trauma or overuse cannot be denied. In the other cases, such a definite traumatic etiology could not be established, though it seems to be of more than casual significance that the prominence of the pisiform bone, into which the flexor carpi ulnaris tendon is inserted, is the area which is normally brought into contact with the desk or table top. It is comprehensible, therefore, that this region may be subjected to traumas of such a minimal nature as to be unremembered and unrecognized, while still causally related to the onset of symptoms. Because of the abrupt mode of onset of the symptoms and their rapid subsidence under treatment, a traumatic origin seems likely, but an underlying focus of infection, a rheumatic diathesis or a metabolic disturbance cannot be categorically excluded.

Apart from the tenderness, swelling and limitation of motion which have been described in the case histories, the characteristic feature is, of course, the appearance of the radio-opaque substance situated near the pisiform bone. Though we have ventured the diagnosis on a clinical basis, even in the absence of any radiodensity, its presence must be considered as pathognomonic of the condition. The calcific shadow may appear as a delicate lacework or in more solid masses. It may be circular, oval or elongated. In all probability, the size and shape of the shadow depend on the stage of the process and the intensity of the reaction. That the appearance had not been previously noted in thousands of plates examined for other conditions would seem proof of the fact that the calcification was not a casual finding or one which might have antedated or even been the cause of the development of symptoms. This seems to be further substantiated by the fact that the calcification disappeared with the subsidence of the clinical symptoms.

Clinically, the condition must be differentiated from a stenosing tendovaginitis or an acute infectious process, such as cellulitis or osteomyelitis. Roëntgenographically, it must be differentiated from osteomyelitis or periostitis of the pisiform bone, an accessory carpal ossicle,

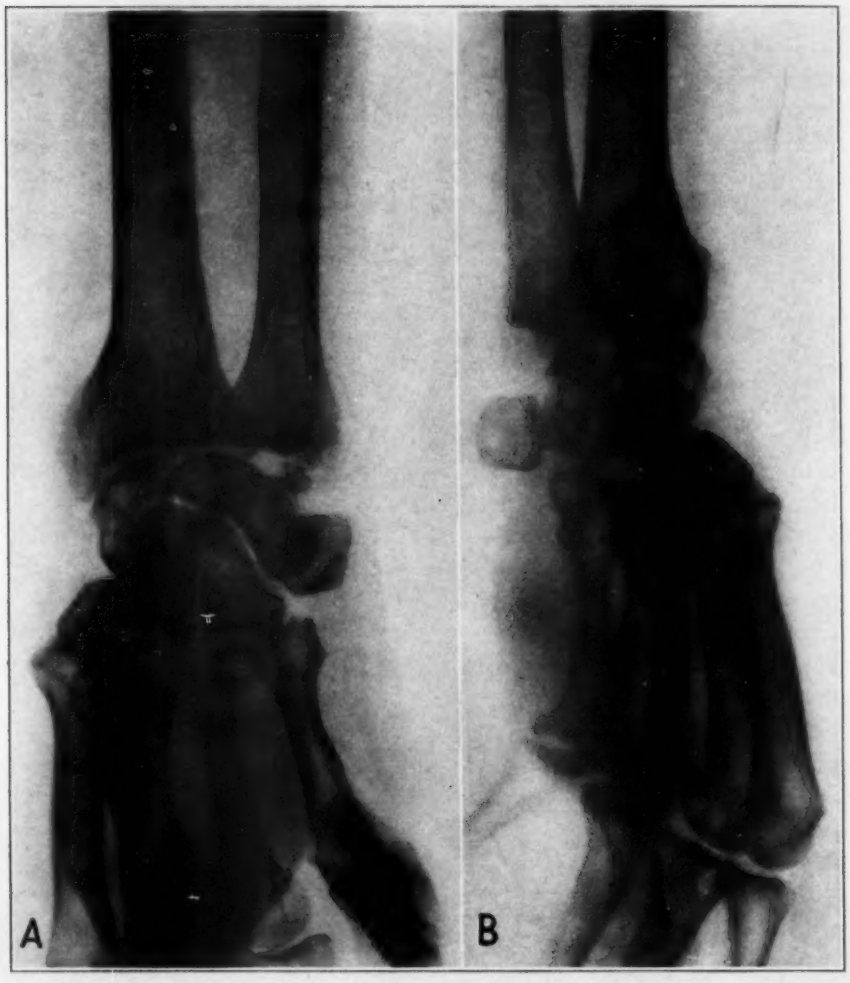

Fig. 6.—*A,* anteroposterior view, showing radio-opacities simulating those seen in the other figures. The patient had a history of a Colles fracture, with fracture of the ulnar styloid process. *B,* on lateral view the radio-opacities were found dorsally and ventrally situated, probably representing fragmentation and healing in a fractured ulnar styloid process.

or an old, comminuted fracture of the ulnar styloid. In the case of one patient whom we recently examined there was a definite history of fracture (fig. 6). Careful lateral and oblique roentgenograms dem-

onstrated conclusively that the ulnar styloid process had been broken at the base and that the calcification was on the dorsal, not the volar, aspect of the wrist. The value of lateral and oblique roentgenograms in all cases cannot be too strongly stressed.

Much as we should welcome the information that would accrue from surgical exploration, we have not found such therapy justifiable. Usually, simple rest on a splint, application of heat and administration of salicylates have resulted in prompt disappearance of the symptoms. It appears that in cases in which the symptoms have been prolonged and in which surgical intervention has finally led to cure the pathologic process has been located in the peritendinous tissue. Though we are not prepared to defend this thesis, the therapeutic response may represent a fundamental pathologic difference and may be a means of clinically differentiating between tendinitis and peritendinitis.

CONCLUSION

The number of cases reported is not sufficiently large to permit any elaborate conclusions. Nevertheless, we believe that calcification at the insertion of the flexor carpi ulnaris tendon is a distinct clinical entity and that the outlines of the clinical picture will be found to conform in general with that here delineated. We feel justified in believing that the process which has been described is occasionally due to trauma and is similar to that already well known in the supraspinatus and gluteal muscles. We are of the opinion that the condition is localized not in the bursa but in the tendon. Though the process is not suppurative, in the acute phase it may give rise to lymphangitis and a febrile reaction and may simulate a destructive process of the pisiform bone. The condition is of short duration and apparently always yields readily to treatment with heat, immobilization and salicylates.

NOTE.—Since this paper was submitted for publication five similar cases have been called to our attention. The details are not presented, since they add nothing to what has already been said.

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CHANGES IN THE MAMMARY GLAND OF THE RAT PRODUCED BY VARIOUS GLANDULAR PREPARATIONS

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During our recent investigation [1] of the influence of endocrine substances on the development of the mammary gland of the rat, a number of mammary abnormalities were experimentally induced. The possibility that some of these observations may have a bearing on diseases of the human breast made it desirable to study the changes further.

It is our purpose in this paper to present the more pertinent results and to suggest their possible relation to mammary disease in human beings.

A number of workers have observed abnormalities in the mammary glands of animals into which various endocrine substances were injected. Evans and Simpson [2] noted extensive mammary development following injection, for long periods, of pituitary extracts into rats; excessive epithelial proliferation and formation of fibro-adenoma occurred in noncastrated females. No effect was obtained in castrates, since the changes are mediated through an effect on the ovaries. Howard [3] recently obtained similar results in noncastrated adult female rats treated for several months with pituitary preparations or with extracts of the blood of pregnant women.

Marked abnormalities of the mammary gland resulting from excessive estrogenic stimulation have been reported. Goormaghtigh and

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This study was aided by a grant from the Anna Fuller Fund.

From the Surgical Pathological Laboratory, Department of Surgery, Johns Hopkins Hospital and Johns Hopkins University School of Medicine.

1. Astwood, E. B.; Geschickter, C. F., and Rausch, E. O.: Development of the Mammary Gland of the Rat: A Study of Normal, Experimental and Pathologic Changes and Their Endocrine Relationships, Am. J. Anat. **61**:373, 1937.

2. Evans, H. M., and Simpson, M. E.: Hormones of the Anterior Hypophysis, Am. J. Physiol. **98**:511 (Oct.) 1931.

3. Howard, N. J.: Comparative Studies of Gonadotropic Hormones: V. Growth Response of Rat Mammary Glands in Chronic Experiments, Proc. Soc. Exper. Biol. & Med. **34**:732 (June) 1936.

Amerlinck [4] produced dilatation of the ducts and adenomatous formations in mice given small doses of estrogen for long periods. Burrows [5] found that continued treatment of mice with estrogen caused the appearance of clusters of acini, dilatation of the ducts, cysts, hyperplasia of the epithelium of the ducts and an increase in stroma. He expressed the opinion that such a series of events is analogous to the chronic cystic mastitis of human beings and stated that mice so treated are more liable to the development of cancer than are nontreated animals. Bonser [6] found that of male mice treated with estrogen, the strains susceptible to cancer showed localized acinar proliferation with subsequent development of cancer while in the strains not susceptible there developed a widespread acinar proliferation without malignant change. Macdonald [7] observed dilatation of the ducts with epithelial proliferation in rabbits treated for three months with estrogen. When such treatment was continued for six months the abnormalities disappeared, and the hypertrophied glands regressed to the resting state, despite continued administration of estrogen. Cystic changes in the mammary glands of rats were obtained by Herold and Effkemann.[8] Gardner, Smith and Strong [9] showed that large doses of estrogen in rats caused a stunted growth of mammary ducts with excessive epithelial proliferation, lobular growth, cystic dilatation of ducts and the appearance of adenomatous areas. Geschickter, Lewis and Hartman [10] induced abnormal mammary growth in the male monkey by the administration of estrogen.

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4. Goormaghtigh, N., and Amerlinck, A.: Realisation expérimentale de la maladie de Reclus de la mamelle chez la souris, Bull. Assoc. franç. p. l'étude du cancer **19**:527 (July 15) 1930.

5. Burrows, H.: Pathological Changes Induced in the Mamma by Estrogenic Compounds (Hunterian Lecture), Brit. J. Surg. **23**:191 (July) 1935.

6. Bonser, G. M.: Effect of Estrone Administration on the Mammary Glands of Male Mice of Two Strains Differing Greatly in Their Susceptibility to Spontaneous Mammary Carcinoma, J. Path. & Bact. **42**:169 (Jan.) 1936.

7. Macdonald, I. G.: Response of the Mammary Gland to Prolonged Stimulation with Ovarian Hormones, Surg., Gynec. & Obst. **63**:138 (Aug.) 1936.

8. Herold, L., and Effkemann, G.: Beziehungen des Follikelhormons zu pathophysiologischen Wachstumsvorgängen der Brustdrüse: I. Brustdrüsenentwicklung unter gesteigerter Zufuhr von Follikelhormon bei der Ratte, Arch. f. Gynäk. **163**:85, 1936; II. Tierexperimentelle Untersuchungen über die Bedeutung einer langdauernden und vermehrten Follikelhormonwirkung in der Genese der Fibrosis mammae cystica, ibid. **163**:94, 1936; III. Unterschiedliche Wirkung einer langdauernden Follikelhormonzufuhr auf die Brustdrüsenstruktur kastrierter und nichtkastrierter Ratten, ibid. **163**:309, 1936.

9. Gardner, W. U.; Smith, G. M., and Strong, L. C.: Stimulation of Abnormal Mammary Growth by Large Amounts of Estrogenic Hormone, Proc. Soc. Exper. Biol. & Med. **33**:148 (Oct.) 1935.

10. Geschickter, C. F.; Lewis, D., and Hartman, C. G.: Tumors of the Breast Related to the Estrin Hormone, Am. J. Cancer **21**:828 (Aug.) 1934.

The effect of estrogen on the incidence of mammary cancer has been variously reported. Lacassagne[11] in an extensive series of articles described the effect of estrogen on male mice of certain strains, the females of which are highly susceptible to spontaneous cancer of the breast. These males, after extensive development of the mammary gland similar to that of normal females, showed epithelial proliferation, dilatation of the ducts and, after six to eighteen months, malignant change. These experiments seem to show that the feminization of males with mammary development places them in the genetic category of their sisters and that both males and females inherit the predisposition to cancer. Similar results have been obtained by Cramer and Horning[12] and by Gardner, Smith, Allen and Strong.[13] This subject has been thoroughly covered recently by Suntzeff, Burns, Moskop and Loeb,[14] who found that treatment with estrogen modifies the incidence of mammary cancer in susceptible strains. It has not yet been established that estrogenic treatment will initiate the formation of cancer in otherwise nonsusceptible animals.

The relation of mammary diseases in human beings to abnormalities of the female reproductive organs has recently been reviewed by Taylor,[15] who attempted to correlate pain in the breast and formation of tumor with ovarian dysfunction. These studies should lead to further investigation of the mammary changes which so commonly occur in persons who present other evidence of endocrine dysfunction.

VARIATIONS IN MAMMARY STRUCTURE

An important consideration in the evaluation of abnormal changes in the breast is variation in the histologic picture and in the physiologic response in different portions of the same breast. In the human breast structural differences in various parts of the gland are difficult to interpret because of the complex distribution of the ducts and the density

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11. Lacassagne, A.: Hormonal Pathogenesis of Adenocarcinoma of the Breast, Am. J. Cancer **27**:217 (June) 1936.

12. Cramer, W., and Horning, E. S.: Experimental Production of Estrin of Pituitary Tumors with Hypopituitarism and of Mammary Cancer, Lancet **1**:247 (Feb. 1) 1936.

13. Gardner, W. U.; Smith, G. M.; Allen, E., and Strong, L. C.: Cancer of the Mammary Glands Induced in Male Mice Receiving Estrogenic Hormone, Arch. Path. **21**:265 (March) 1936.

14. Suntzeff, V.; Burns, E. L.; Moskop, M., and Loeb, L.: Effect of Injections of Estrin on the Incidence of Mammary Cancer in Various Strains of Mice, Am. J. Cancer **27**:229 (June) 1936.

15. Taylor, H. C., Jr.: Relation of Chronic Mastitis to Certain Hormones of the Ovary and Pituitary and to Coincident Gynecological Lesions: I. Theoretical Considerations and Histological Studies, Surg., Gynec. & Obst. **62**:129 (Feb.) 1936; II. Clinical and Hormone Studies, ibid. **62**:562 (March) 1936.

of the enveloping fibrous tissue; but that such local differences exist is shown, for example, by the frequency of certain changes in the outer upper quadrant of the breast and by the fact that markedly different histologic pictures can be seen in a single microscopic preparation from apparently normal breast tissue.

In the normal rat structural differences in various areas of the same mammary gland are very distinct. When the animal is subjected to certain endocrine stimuli, the structure of these areas departs still further from the normal. In the region near the nipple where the single main duct divides into its several larger branches there is a maximum number of small twigs and buds, which respond to estrogenic stimuli

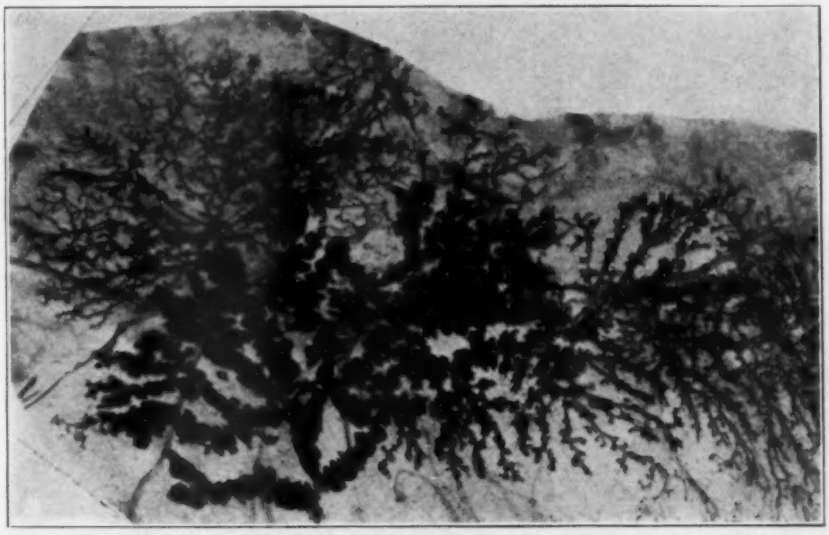

Fig. 1.—Whole mount (× 5⅓) of two mammary glands from a 115 day old female rat treated from birth with 0.25 mg. of testosterone propionate daily. The difference in response in different areas is well shown. The central areas resemble those of the normal male structure, while the periphery is typically female in appearance.

with the formation of small, imperfectly shaped lobules. Throughout the major portion of the gland in the normal female the ducts are regularly distributed and show frequent branching and an even scattering of fine twigs. In the outermost borders of the gland—and this is especially true of the dorsal prolongation of the large abdominal gland—the ducts are irregular, fine and relatively bare; they respond in a limited manner to estrogenic stimuli and, as noted by Maeder,[16] even to the

16. Maeder, L. M. A.: Changes in the Mammary Gland of the Albino Rat (Mus Norvegicus Albinus) During Lactation and Involution, Am. J. Anat. **31**:1 (Sept.) 1922.

Fig. 2.—Whole mount (× 18) of a mammary gland of a normal 75 day old female rat, showing the normal postpuberal architecture characteristic of the non-pregnant adult female.

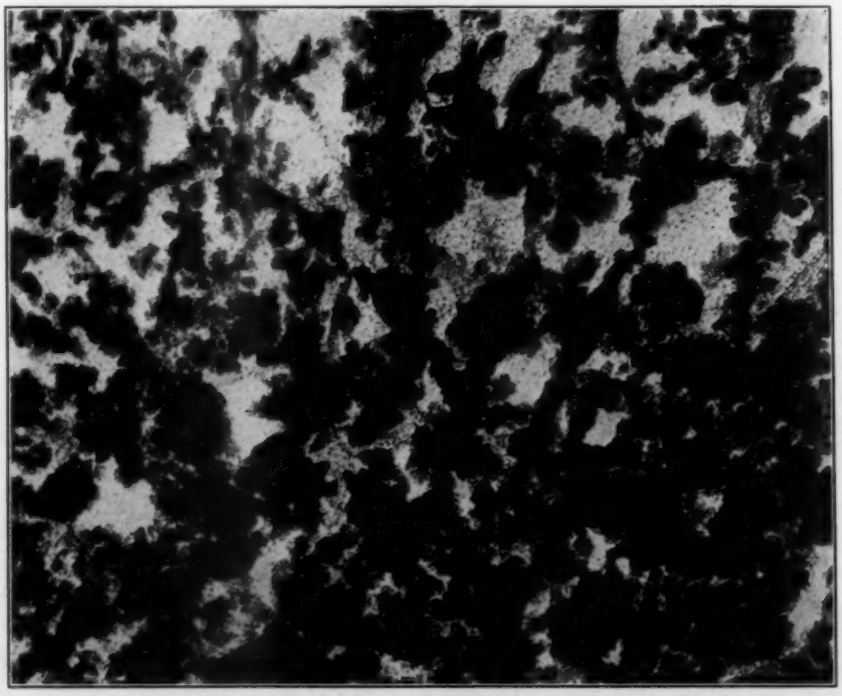

Fig. 3.—Whole mount (× 18) of a mammary gland of a normal 75 day old male rat, showing the characteristic dense structure made up of lobule-like acinar clumps.

stimulus of pregnancy. When normal this region is easily mistaken for a region of regression. Figure 1 shows a mammary gland of a female rat treated from birth with 250 micrograms of testosterone propionate for one hundred and fifteen days. The central area near the nipple, consisting largely of the main ducts, has responded well to the androgenic stimulus, while the peripheral regions show little effect of the preparation.

SEXUAL DIFFERENCES

Differences between the early development of the male and that of the female breast, as noted by Myers,[17] consist chiefly in the distribution of the main ducts. In most respects development during early life is identical in the two sexes; marked sexual differences in the rat appear after six weeks under the influence of the developing gonad, as described by Turner and Schultze.[18] In the female the influence of the developing ovary results in a rapid extension of the duct tree and a multiplication of fine twigs (estrogenic stimulation), as seen in figure 2, while in the mature male the finer mammary ducts terminate in a proliferation of acinar elements, which results in the small dense gland characteristic of the adult male rat (influence of androgen), as seen in figure 3. In animals which are castrated at the age of 21 days, increase in size is not interfered with during the next three weeks; but after the sixth week of life the glands begin to grow more slowly, and after the eighth week they show signs of regression. At this stage differences between the male and female glands are most marked. The female gland shows a profusion of extremely fine branched ducts, which cover an extensive area, while the male gland, smaller in extent, is composed of thicker, more irregular and less numerously branched ducts (figures 4 and 5). These differences are entirely independent of the gonad and must be classed as genetic sexual differences. Such sexual differences undoubtedly are present also in the human being, and one might expect unsimilar responses in the two sexes to administration of glandular preparations. This has already been indicated by the unusual type of mammary growth occasionally induced in the human male by large doses of estrogen.[10]

The changes effected in the breast by an endocrine stimulus are dependent as much on the inherent behavior of the breast as on the nature of the stimulus. In general, the male breast responds to estrogenic stimuli in a manner comparable to that of the female, that is,

17. Myers, J. A.: Studies on the Mammary Gland: III. A Comparison of the Developing Mammary Glands in Male and Female Albino Rats from the Late Fetal Stages to Ten Weeks of Age, Anat. Rec. **13**:205 (Sept.) 1917.

18. Turner, C. W., and Schultze, A. B.: A Study of the Causes of the Normal Development of the Mammary Glands of the Albino Rat, Research Bulletin 157, University of Missouri, College of Agriculture, Agricultural Experiment Station, 1931.

Fig. 4.—Whole mount (× 18) of a mammary gland of a 75 day old female rat whose ovaries were removed at the age of 21 days. The ducts are fine and bare and do not show the profusion of fine twigs and buds which result from ovarian maturation, as seen in figure 1.

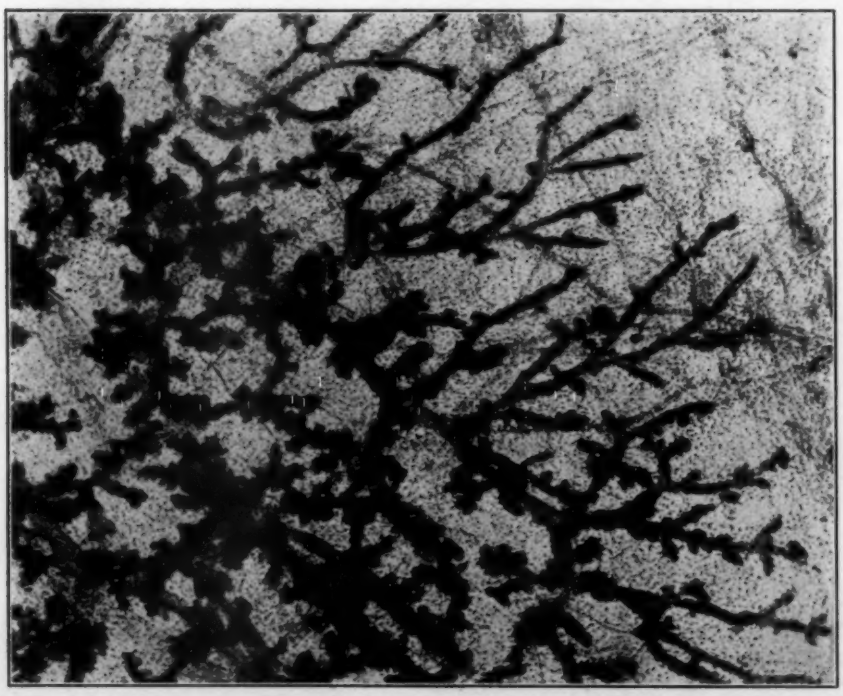

Fig. 5.—Whole mount (× 18) of a mammary gland of a 75 day old male rat castrated at the age of 21 days. The ducts are wider and possess more clublike branches and buds than those of the castrated female shown in figure 2. The dense growth of lobule-like structures due to testicular influence is not present. Compare with figure 3.

through extension and increased branching of the duct tree. In a series of experiments with the undeveloped glands of immature animals, little difference can be seen in the effect of estrogen on the male and on the female. When estrogen is administered for longer periods, some differences become apparent. The male glands show a greater tendency to form clumps of alveolar structures, while the female glands respond by more marked extension of the duct tree.

Thus the difference in structure and in manner of response in various portions of the same gland and the difference between the behavior of the glands in male and female castrates show that a large part of the response mechanism rests in the gland itself and is entirely independent of the stimulus to growth. This local variation in response must be constantly borne in mind when one is interpreting the abnormalities experimentally induced, particularly in the evaluation of the results of studies of the human mammary gland.

EXCESSIVE ESTROGENIC STIMULATION

The typical effect of estrogen on the mammary gland is well shown in the immature rat; there is an easily recognizable extension of the duct tree, with increased branching. This response is characteristic of estrogenic stimulation, is distinct from other hormonal effects and is a sensitive index of estrogenic activity, 1 international unit of estrogen given daily producing a notable effect. This physiologic effect of estrogen on the breast in causing extension of the duct tree appears to be common to all species studied. In the human being a similar response is seen in the rapid growth of ducts early in puberty in the female. The human breast, however, possesses a large amount of fibrous stroma and in this respect is peculiar among mammals. Therefore, the mechanism of this growth of fibrous tissue cannot be adequately studied in any mammal except the human being.

The lobular formation of pregnancy cannot be produced in the castrated rat by estrogen alone, this substance merely producing an extension of the system of ducts, with a profusion of fine twigs and buds. That is to say, estrogen produces a mammary gland typical of the adult female virgin state, while the changes of pregnancy are due to mechanisms which are as yet poorly understood. In certain species, for example, the guinea pig,[19] estrogen alone is capable of stimulating formation of lobules. We have found this to be the case in monkeys at puberty, and it seems probable that it is also true of the human being.

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19. Nelson, W. O.: Studies on the Physiology of Lactation: VI. The Endocrine Influences Concerned in the Development and Function of the Mammary Gland in the Guinea Pig, Am. J. Anat. **60**:341 (March) 1937.

Giving more than the physiologic dose of estrogen or prolonging administration results in certain constant and definite abnormalities. These are probably due not to a direct action of estrogen but rather to a profound upset in the endocrine mechanism which controls mammary growth. Large doses of estrogen show their earliest effects in causing a stunted type of growth. The duct tree is less extended than with small doses and becomes more irregular; the ducts are distorted and widened, with irregular club-shaped twigs along their length. From the first there is evidence of excessive epithelial growth, especially in the

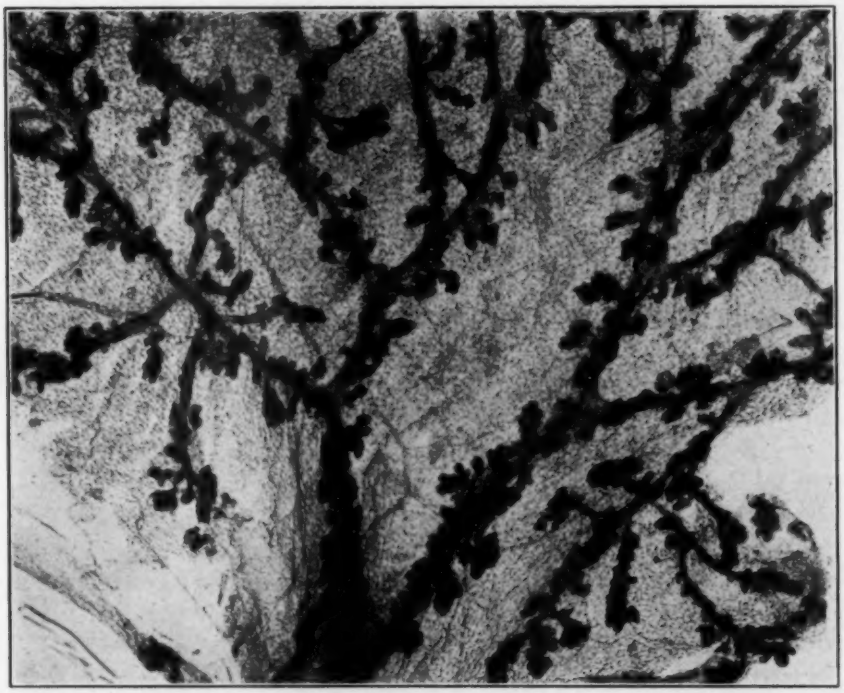

Fig. 6.—Whole mount (× 18) of a mammary gland of a female rat castrated at the age of 21 days and treated for nine days with 100 micrograms of estrone daily, showing the earliest effect of high doses of estrogen. The ducts are widened, and there is excessive proliferation of buds and short branches. The gland was restricted in area.

terminal buds and smaller twigs, and accompanying this growth there appears evidence of secretory activity. Figure 6 shows the breast of a rat castrated at the age of 21 days and treated for nine days with 100 micrograms of estrone daily; the widening of the short, irregular ducts and the accumulation of budlike projections can be seen. This early dwarfing can be readily accentuated by more vigorous treatment; it is distinctly pathologic.

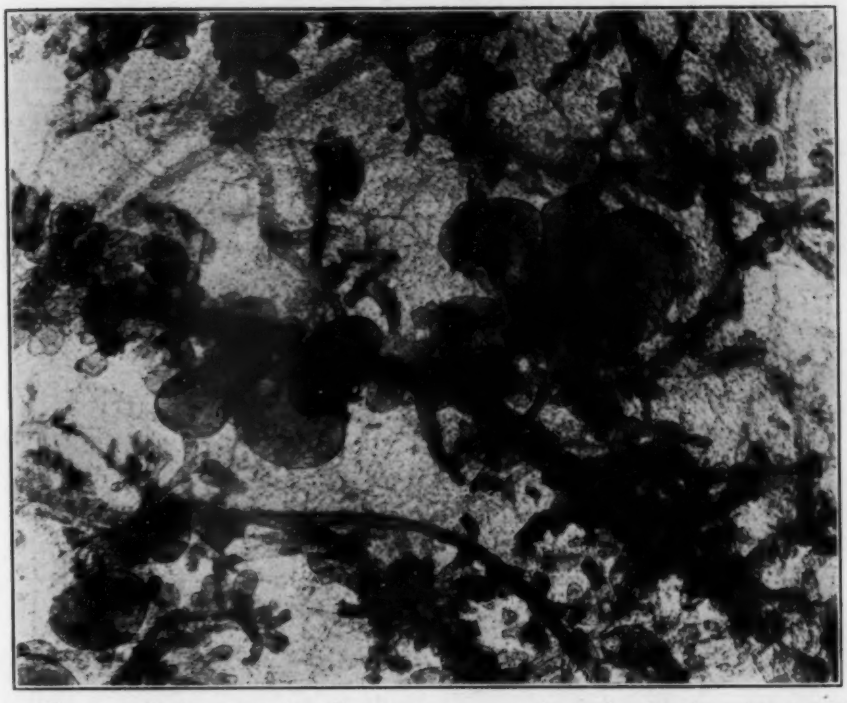

Fig. 7.—Whole mount (× 18) of a mammary gland of a female rat castrated at the age of 21 days and given 200 micrograms of estrone daily for fifty-six days, showing the formation of cysts in the terminal buds and side branches of the moderately dilated ducts.

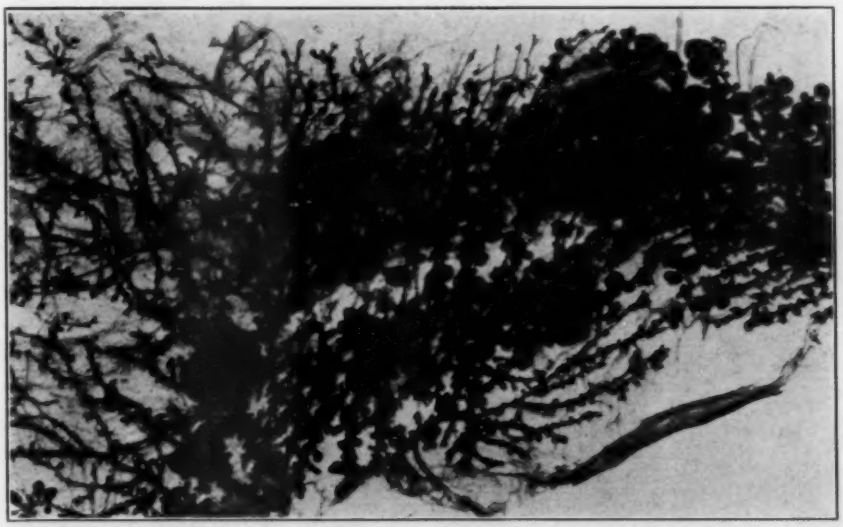

Fig. 8.—Whole mount (× 5⅓) of a mammary gland of a female rat castrated at the age of 21 days and given 200 micrograms of estrone daily for one hundred and fifty days, showing an advanced stage of cyst formation. The larger cysts appear as dark areas and the smaller ones as small grapelike clusters. The cysts (fig. 10) contain coagulated secretion and are lined by proliferting epithelium. An unaffected area is seen in the usual refractory zone on the left.

Fig. 9.—Whole mount (× 3) of a mammary gland of a rat castrated at the age of 21 days and given 50 micrograms of estrone daily for one hundred and ninety-three days, showing the formation of small cystic dilatations and irregular epithelial buds resulting from prolonged dosage with moderate amounts of estrogen.

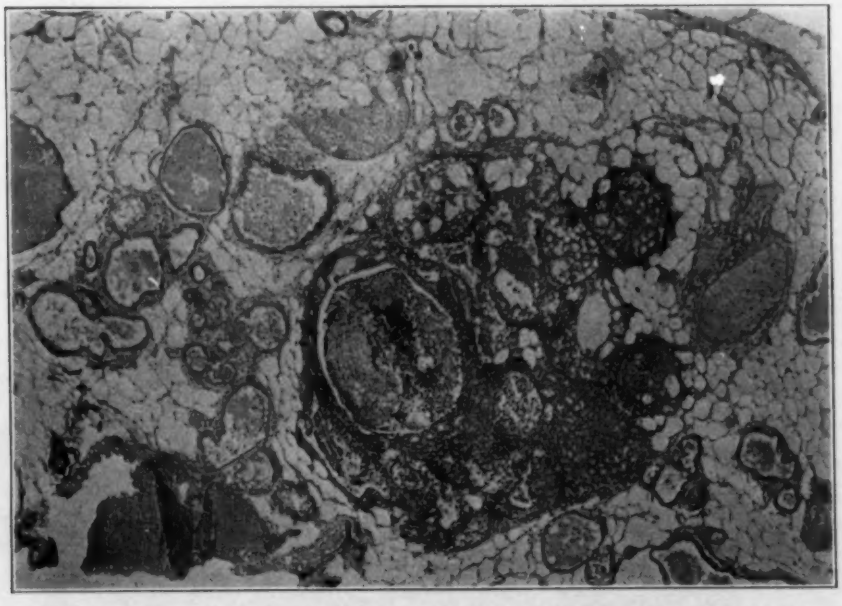

Fig. 10.—Paraffin section (× 27) of a portion of the mammary gland shown in figure 8. In this area the small cysts are nearly filled with epithelial growth and small papillomas. The picture is not unlike that of Schimmelbusch's disease in human beings.

When such excessive doses of estrogen are continued, marked evidence of secretion becomes manifest. The ducts become widened; the budlike projections are distended, and cysts of all sizes appear. These

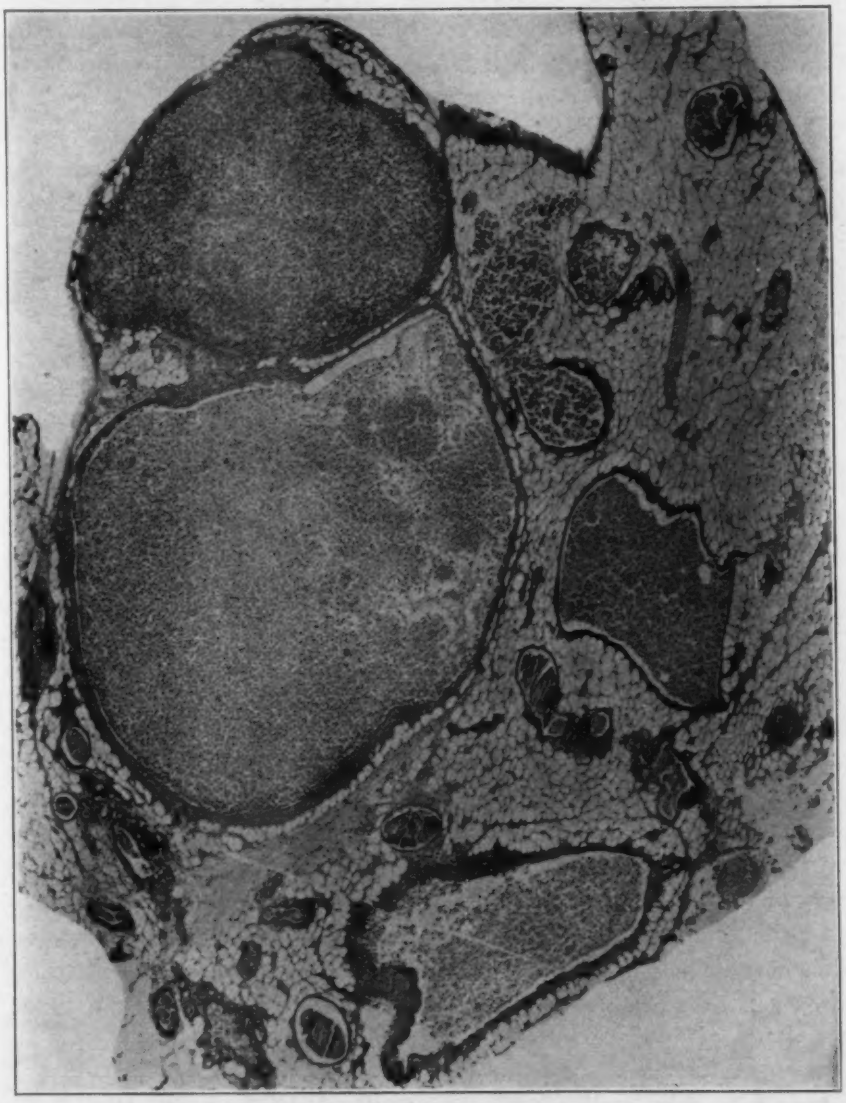

Fig. 11.—Paraffin section (× 27) of a mammary gland from the animal shown in figures 8 and 10. The largest cyst possesses a thick fibrous wall without an epithelial lining, while the smaller shows a proliferation of fibroblasts invading the contained secretion. The smallest cysts still possess a single orderly layer of epithelium.

cysts are formed in the termini of the ducts, in those structures destined normally to form acini. Figures 7 to 11 inclusive show the appearance

of this cystic change. It can be seen that the smaller cysts are lined by a single layer of epithelium and that their lumens, filled with dense secretion, are in direct communication with the ducts, which are distended with a like secretion. In some areas, after prolonged overstimulation with estrogen, there is excessive epithelial growth in the ducts and in the cyst walls, resulting in a heaping up of cells and papillomatous growths (fig. 10). As the cysts become larger and older they lose their epithelial lining, and the enveloping fibrous tissue becomes more dense, surrounding the cavity as a thick wall. At this stage the original communication of the cyst cavity with the lumen of the duct is lost, and the contents can no longer be expressed without rupture of the cyst wall. Some of the cysts show excessive proliferation of fibrous tissue in their walls, while invasion of the lumen by fibroblasts gives the appearance of organization of the contained secretion (fig. 11). These cystic changes have been constantly observed in all animals receiving 100 or more micrograms of estrone daily for periods of three weeks or more, and in those animals given 50 micrograms daily for longer periods, in which they occur less often or are smaller. It has been found that the higher the dose, the more quickly the cysts develop, and the more marked is the degree of abnormal change. In animals receiving these large doses of estrogen the cystic changes can be prevented, as will be seen later, by administering other hormones.

Smaller doses of estrone given over long periods result in a different type of mammary change. Doses such as 25 micrograms daily or 100 to 200 micrograms *weekly* produce a primary stimulation of development of duct and terminal tubules marked by evidence of excessive epithelial growth. Secretory phenomena are minimal; only after long periods of treatment are cystic dilatations noted, and even then they are not marked. Instead, the primary picture of estrogenic stimulation gradually gives way to the appearance of regressive changes. The mammary gland becomes more and more varied in its architecture, and the differences noted in different regions of the normal gland are greatly accentuated. Certain regions show marked involution, with narrow, crooked bare ducts; in other regions the ducts are distended with clear secretion, and their budlike projections are dilated into microscopic cysts. Scattered throughout most of the gland are isolated areas of terminal tubular proliferation resulting in clumps of imperfectly formed lobules; occasionally one or two normal-appearing lobules made up of discrete alveoli are seen. Figure 12 shows an area of excessive epithelial proliferation in a castrated female rat treated from the twenty-

first day of life with 25 micrograms of estrone daily for fifty-six days. The growth of terminal tubules is extremely irregular; in some places clumps of tubules form dense epithelial masses, while in others, discrete lobules result; some of the ducts are devoid of tubular growth for a part of their length. Other areas of this same mammary gland showed marked regression similar to that of the castrated female rat pictured in figure 4. Treatment with estrogen for long periods produces an increase in the amount and density of the periductal connective tissue. Normally very

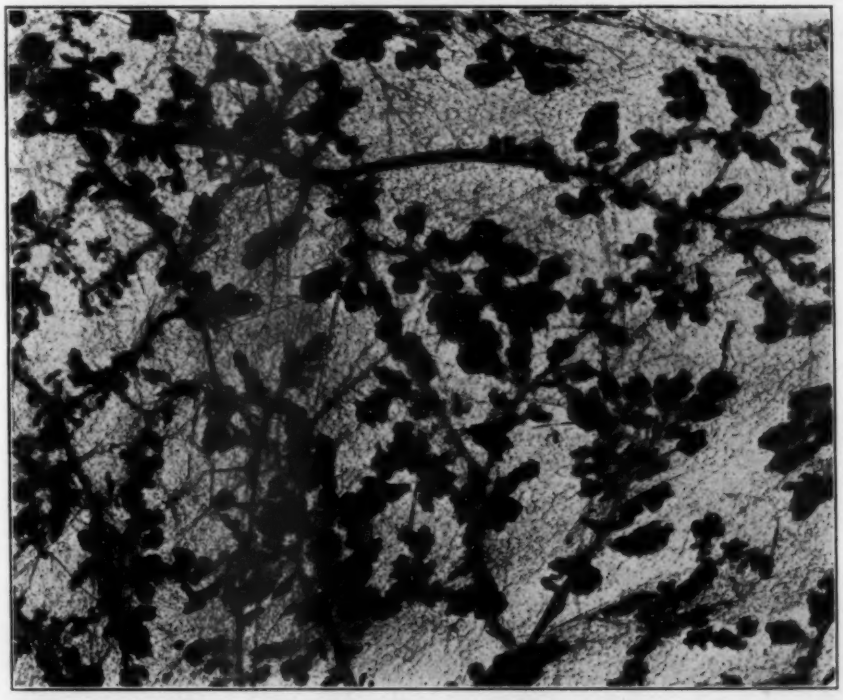

Fig. 12.—Whole mount (× 18) of a mammary gland of a female rat castrated at the age of 21 days and given 25 micrograms of estrogen daily for fifty-eight days, showing an area of extensive epithelial proliferation. The lobule-like structures are irregular and isolated, leaving many parts of the ducts bare. Other regions in this gland resembled regions seen in figure 4.

fine and areolar, scarcely demarcating the duct from the surrounding fatty stroma of the breast, the periductal connective tissue becomes thickened and opaque, encasing the ducts in a dense tube of fibrous tissue. This change is most marked near the nipple, around the larger ducts, becoming less perceptible toward the periphery of the gland. Figures 13 and 14 show increased connective tissue, around the main ducts, small

cysts, areas of epithelial proliferation and adenoma-like formation in a rat treated for six months with 50 micrograms of estrogen daily.

The changes which follow the administration of various amounts of estrogen are similar to that group of conditions in the human breast included in the term chronic mastitis. The pathologic changes of these diseases of the breast are extremely varied, but there is reason to believe that they are all attributable to a single mechanism, and for the most part the individual changes are but different degrees and different stages of the same abnormal process. Although proof is lacking, it would

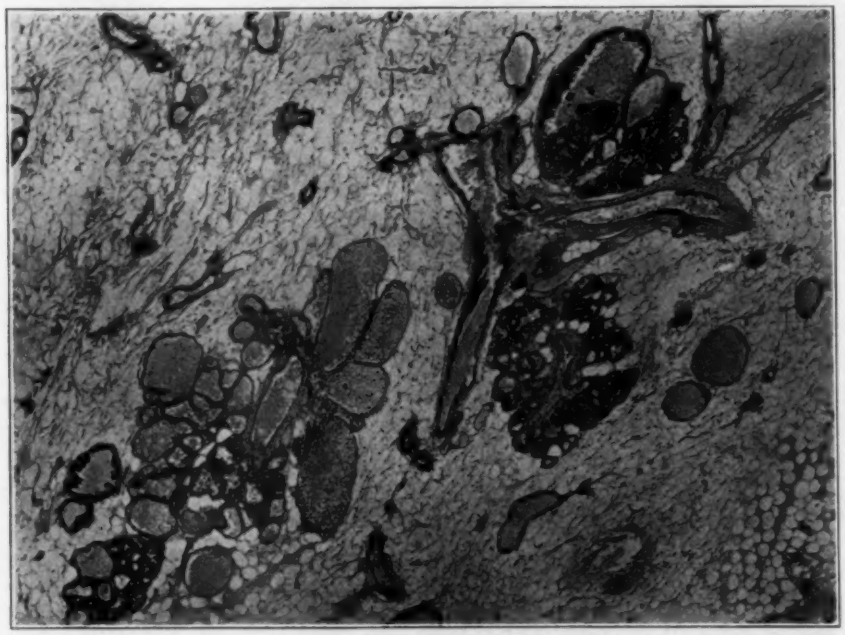

Fig. 13.—Paraffin section (× 27) of a mammary gland of a female rat castrated at the age of 21 days and given 50 micrograms of estrogen daily for one hundred and eighty-five days. In this area can be seen dilatation of the ducts, with increased periductal connective tissue, cystic formation, excessive intracystic epithelial proliferation and an area of adenomatous growth.

appear that the formation of large cysts in the breasts of rats given more than 100 micrograms of estrone daily for several months is analogous to that form of cystic disease characterized by the presence of a limited number of large cysts (the blue-domed cyst of Bloodgood). In this condition there is little formation of lobules, and a minimum of epithelial proliferation occurs.

Those histologic changes in the breast of the rat which result from the administration of estrogen for longer periods, i. e., for six months or more, in smaller doses closely resemble the more diffuse mammary

changes common to the earlier phases of all forms of chronic cystic mastitis. In these cases there is great variation in the histologic picture, which in different regions shows dilatation of ducts, cyst formation, epithelial proliferation with intracystic papillomas, areas of

Fig. 14.—Paraffin section (× 27) of a mammary gland of the rat from which was taken the section presented in figure 13, showing an area around the larger ducts near the nipple, where there is a considerable increase in periductal connective tissue.

lobule formation resembling localized adenomas and a generalized increase in fibrous stroma. The marked epithelial proliferation in the animals which receive estrogen for long periods resembles that seen in

the form of chronic cystic mastitis first described by Schimmelbusch, in which the small mammary gland with its short ducts shows extensive epithelial overgrowth, formation of adenomas and papillomas being concurrent with the cystic change. It must be remembered, however, that in the human being there is a difference in response to estrogen on the part of the fibrous stroma and of the lobular epithelium. The lobular growth, as demonstrated in the monkey, may respond more readily to stimulation by the corpus luteum hormone. Therefore, too close a parallel cannot be drawn between the mammary changes in the human being and those experimentally induced in rats.

EFFECTS OF STIMULATING THE GONADS

In contrast to the extension of the duct tree produced by the action of estrogen on the breast, the effect of gonadotropic substances on the intact female is the occurrence of the true changes of pregnancy, with formation of lobules. When the gonadotropic substance from the urine of pregnant women or the gonad-stimulating substance of urine taken from women after the menopause is administered to the rat, marked ovarian enlargement resulting from the formation of numerous large corpora lutea occurs. The mammary glands of animals whose ovaries are thus stimulated are indistinguishable from those of a pregnant animal at full term. Continuation of such treatment will not maintain the mammary gland in such a condition for long periods, for after a month or two the animal becomes refractory to the injected substance, the ovaries decrease in size and the mammary glands regress. The degree to which regression occurs varies greatly in different animals and with different gonadotropic preparations. In most cases involution begins between the first and the second month of injection and slowly continues for a month or more. In some cases the involuted gland is scarcely distinguishable from that of the normal, nontreated animal, but usually there is notable increase in the periductal connective tissue, and frequently there are residual areas of incomplete regression. Figure 15 shows the residual increase in connective tissue after prolonged administration of gonadotropic substance. Sometimes incompletely involuted areas stand out in contrast to the surrounding structures and may be confused with true adenoma or fibro-adenoma.

It is interesting that in animals whose mammary glands are maintained in a state similar to that of pregnancy high doses of estrogen do not produce cystic changes. As has been shown, a daily dose of 100 micrograms or more of estrone resulted in formation of cysts within three weeks in every case. When noncastrated animals are given gonadotropic substances during the period of administration of estrogen, the mammary glands show lobular development and the full changes of preg-

nancy; formation of cysts with its accompanying changes does not take place, and as long as the changes of pregnancy are maintained no cystic transformation occurs. Figure 16 shows a section from a noncastrated rat treated from the twenty-first day of life with 200 micrograms of estrone daily for eighty-one days and at the same time with 50 rat units of gonadotropic substance from the urine of pregnant women. Despite the

Fig. 15.—Paraffin section (× 27) of a mammary gland of an intact female rat treated from the twenty-first day of life with 50 rat units of gonadotropic substance from the urine of pregnant women for ninety-two days. The lobular growth in this rat has regressed, leaving the ducts bare but surrounded by dense hyaline connective tissue.

vigorous treatment with estrogen, no cysts were produced. The lobular formation had regressed considerably below its maximum size, which was noted after about three weeks of treatment, and there was beginning increase in fibrous stroma; but there was no perceptible difference between this gland and the glands of animals treated with gonadotropic

substance alone. It is not until an animal becomes refractory to the gonadotropic substance that cyst formation begins to result from the continued injection of estrogen.

The application of these observations to human beings deserves emphasis. As is well known, all forms of chronic cystic mastitis are much less common in multiparous than in nonparous women, and it is not uncommon for the disease to regress during pregnancy and lactation. In two women recently seen in Johns Hopkins Hospital complete symptomatic cure of chronic cystic mastitis occurred during the first half

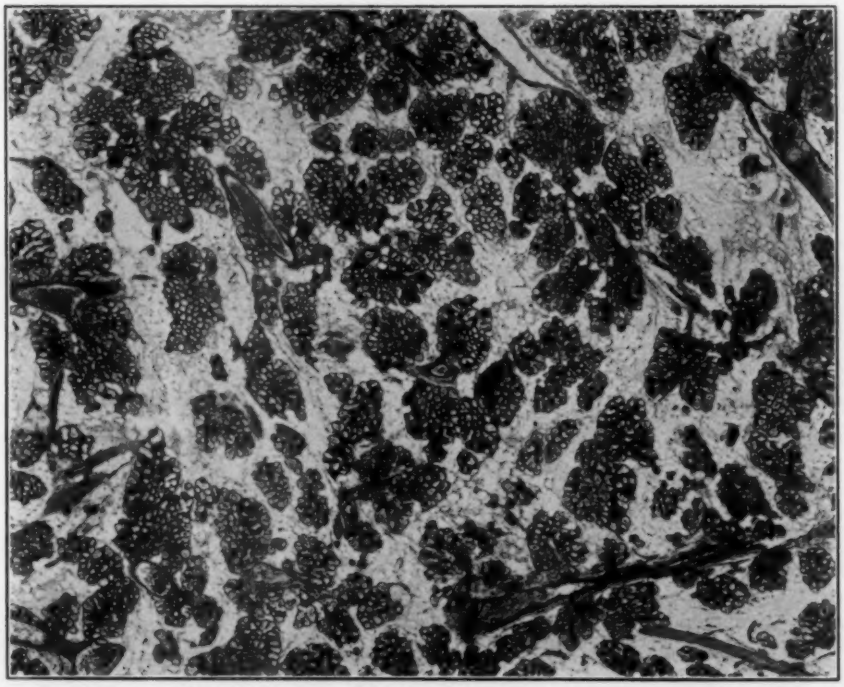

Fig. 16.—Paraffin section (× 18) of a mammary gland from an intact female rat treated from the twenty-first day of life with 200 micrograms of estrogen daily for eighty-one days, together with 50 rat units of gonadotropic substance from the urine of pregnant women daily. The gland shows lobular growth which has partially regressed, but the cystic changes which would have been expected from the high doses of estrogen have been prevented. Compare with figures 7 to 11, which show changes that result from administration of estrogen alone.

of the period of pregnancy.[19b] The artificial induction of the mammary changes of pregnancy would be effective treatment for chronic cystic mastitis in the human being.

19b. Lewis, D. L., and Geschickter, C. F.: Endocrine Therapy in Chronic Cystic Mastitis, J. A. M. A. **109**:1894 (Dec. 4) 1937.

ACTION OF CORPUS LUTEUM

The mammary changes of pregnancy preparatory to lactation have been widely attributed to the action of the corpus luteum hormone. The fact that these changes occur also during other periods when corpora lutea are present in the ovary, as during pseudopregnancy and after the administration of gonadotropic substances, lends strength to such an idea. Some authors [18] have found that the administration of estrogen together with extracts of corpus luteum results in formation of lobules. Our experiments with synthetic progesterone, however, have failed to demonstrate any action of this substance on the mammary gland of the rat. As seen in the table, various amounts of progesterone have been given to rats, with or without previous or concomitant administration of estrogen, without producing any effect on the mammary gland. Although this series of rats is necessarily small because of the inaccessibility of large quantities of progesterone, their mammary glands were carefully studied and compared with a great many controls. Even 5 mg. given daily exerted no action on the breast. Similar failure of mammary response to progesterone in the rat was noted by Selye, Browne and Collip.[20] As it has been possible to show an effect on the mammary gland ascribable to progesterone in rabbits and monkeys, it would seem unwise to draw a parallel between the rat's breast and the human breast in regard to the action of progesterone.

EFFECTS OF ANDROGEN

As first noted by Cooper,[21] the human male mammary gland shows considerable development. Recently Jung and Shafton [22] demonstrated that in a large percentage of boys the mammary glands become palpable at puberty. Selye, McEuen and Collip [23] were the first to show that testosterone exerts an action on the mammary gland of the rat. The normal adult male rat shows a typical mammary structure, one which is never seen normally in the female. This type of growth can be induced in immature males by gonad-stimulating substances. It is prevented by castration in the male and can be reproduced in animals of either sex by administration of androgen. As has already been shown, estrogen produces

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20. Selye, H.; Browne, J. S. L., and Collip, J. B.: Effect of Combined Administration of Estrone and Progesterone in Adult Ovariectomized Rats, Proc. Soc. Exper. Biol. & Med. **34**:198 (March) 1936; Effect of Large Doses of Progesterone in the Female Rat, ibid. **34**:472 (May) 1936.

21. Cooper, A. P.: The Anatomy and Diseases of the Breast, Philadelphia, Lea & Blanchard, 1845.

22. Jung, F. T., and Shafton, A. L.: The Mammary Gland in the Normal Adolescent Male, Proc. Soc. Exper. Biol. & Med. **33**:455 (Dec.) 1935.

23. Selye, H.; McEuen, C. S., and Collip, J. B.: Effect of Testosterone on the Mammary Gland, Proc. Soc. Exper. Biol. & Med. **34**:201 (March) 1936.

extension and increased branching of the ducts, the result being a type of gland normally seen in the female adult. Stimulation of the testis or administration of androgen produces an effect very different from that of estrogen, causing the development of the peculiar, lobule-like structures characteristic of the normal adult male. The human male mammary gland also presents a typical structure consisting of thick, poorly branched ducts lined by several layers of epithelium and enmeshed in a dense fibrous matrix. The excessive mammary development sometimes seen at or soon after puberty and the rarely seen bilateral gynecomastia accompanying tumors of the adrenal cortex possess a similar architecture. It is possible that this hypertrophy results from the action of androgen, as both the maturing testes and hyperactivity of the adrenal cortex are apparently responsible for gynecomastia observed clinically. It has been shown that estrogen will also cause enlargement of the human male breast. However, in a great many cases gynecomastia is unilateral and must be ascribed to some inherent factor in mammary response independent of an endocrine abnormality. When testosterone is administered for long periods to rats, there are a great increase in the epithelium lining the ducts and alveoli and considerable shedding of cells into the lumens of these structures. Figures 17 and 18 show the gross and microscopic structure of a mammary gland of a female rat treated from birth with 250 micrograms of testosterone propionate given daily for forty-two days.

Vest (personal communication), at the Brady Urological Institute of the Johns Hopkins Hospital, has treated a series of eight patients over periods of from three months to a year with injections of testosterone propionate. The patients received doses varying from 50 mg. weekly to 10 mg. daily, the ages being 3½, 9, 23, 27, 31, 32, 33 and 62 years, respectively, at the beginning of treatment. Although all of these patients showed development of the external genitalia and of the prostate, none of them showed any evidence of mammary enlargement. One patient, a 31 year old man, had slight tenderness beneath one nipple and some increased density of fibrous tissue at one examination. This had disappeared, however, one week later and did not recur, despite continuation of the treatment. Kenyon and others [24] in four cases of gynecomastia found normal excretion of estrogen in the urine, but the androgen in the same cases varied from none to normal amounts. One of us (C. F. G.) has performed biopsies in three cases of gynecomastia before and after injections of testosterone in doses ranging from 50 to 150 mg. without observing significant mammary changes.

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24. Kenyon, A. T., and others: Urinary Excretion of Androgenic and Estrogenic Substances in Certain Endocrine States, J. Clin. Investigation **16**:705, 1937.

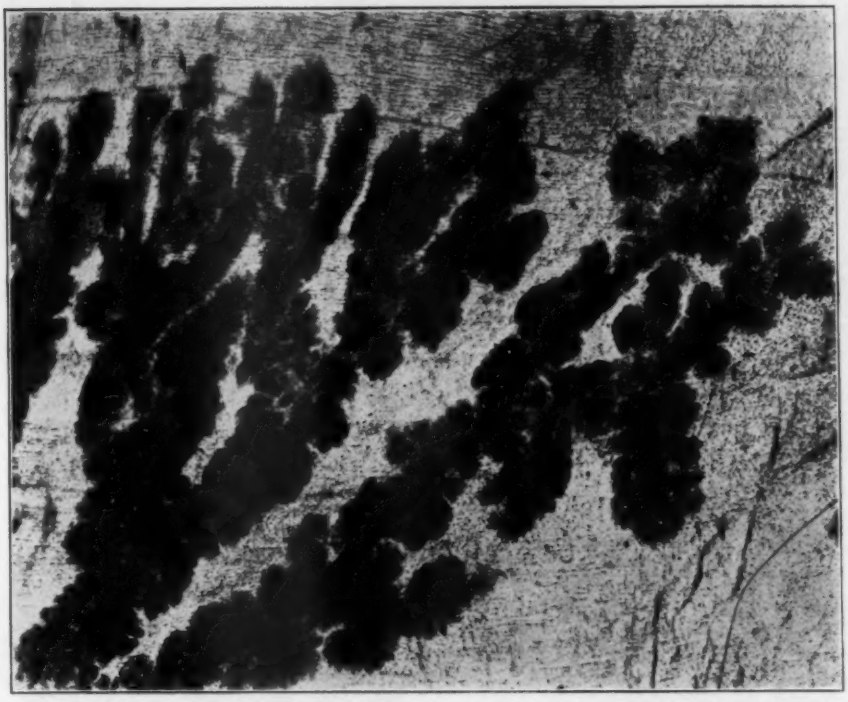

Fig. 17.—Whole mount (× 18) of a mammary gland of a female rat treated from birth with 250 micrograms of testosterone propionate daily for forty-two days. The gland shows a dense proliferation of lobule-like structures similar to those seen in the normal adult male.

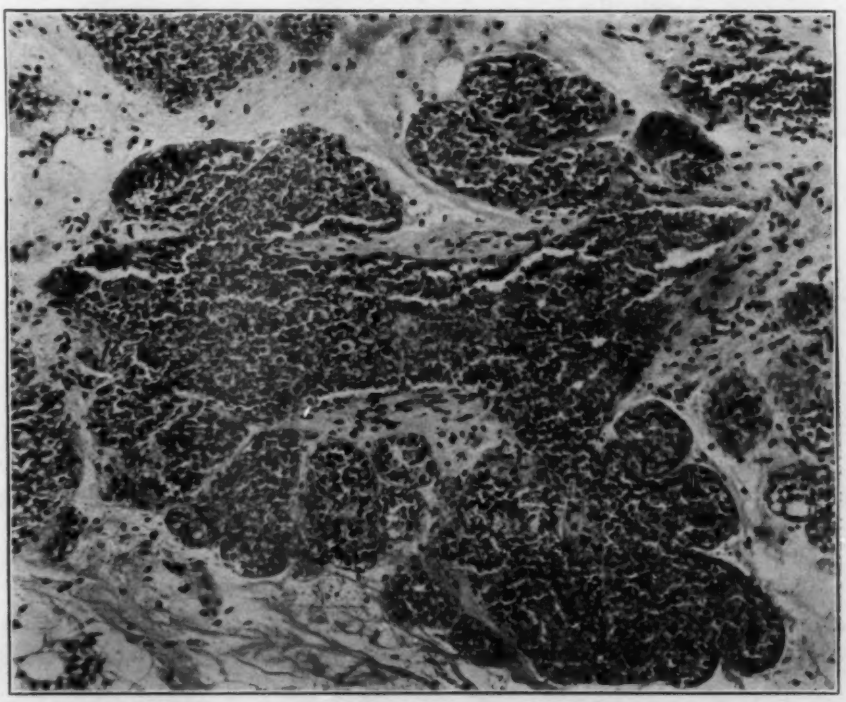

Fig. 18.—Paraffin section (× 150) of a mammary gland from the rat seen in figure 17, showing the extensive epithelial proliferation in the ducts and alveolar structures and the shedding of these cells into the dense secretion in the lumens.

PITUITARY LACTOGENIC SUBSTANCE

It is now definitely established that the actual secretion of milk is under the control of a principle of the anterior lobe of the pituitary gland. A question still to be answered concerns the nature and the extent of the histologic change that is brought about by this substance. More study with the use of potent pituitary substances is necessary

Fig. 19.—Whole mount (× 27) of a mammary gland of a female castrated at the age of 21 days and treated with 100 micrograms of estrogen daily for twenty days followed by administration of 40 bird units of pituitary lactogenic substance daily for five days. The terminal buds, having been rendered abnormal by the administration of estrogen, are diffusely and irregularly distended with secretion.

to determine the effect of the lactogenic substance on the mammary structure.

The secretory changes which follow high doses of estrogen are in part the result of hypermaturation of mammary epithelium and are probably

in part the result of the action of the lactogenic substance elaborated by the animal's own pituitary gland under the stimulus of estrogen. Marked secretory phenomena such as occur in the cysts experimentally produced and in mammary cysts in human beings must be the result of stimuli from secretions of the pituitary gland. The cysts themselves appear to be the result of secretory stimuli acting on a gland already rendered abnormal by the excessive doses of estrogen. Figure 19 shows the result of this action. This female rat castrated at the age of 21 days received 100 micrograms of estrogen daily for twenty days, followed by 40 bird units of pituitary lactogenic substance given daily for five days. As has already been shown, these high doses of estrogen produce

Effects of Progesterone Administered to Female Rats *

		Estrone		Progesterone			
Rat No.	Age at Start, Days	Daily Dose, Micrograms	Duration of Treatment	Daily Dose, Milligrams	Duration of Treatment	Age at Death, Days	Mammary Glands
1	21	100	21st-41st day	0.5	31st-41st day	46	Short, stunted, widened ducts and small buds; high dosage estrogen effect
2	21	10	21st-41st day	0.025	31st-41st day	42	Extended and branched system of ducts
3	21	5	21st-41st day	1.0	33d-41st day	42	Typical effect of estrogen; no lobules
4	21	None	.....	0.25	21st-31st day	32	Normal immature gland
5	21	None	.....	0.25	21st-41st day	42	Normal immature gland
6	21	5	40th-50th day	0.25	21st-50th day	51	Extended system of ducts; no lobules
7	1	50	1st-64th day	0.5	54th-64th day	65	Typical high estrogen dosage effect
8	276	None	.....	0.5	For 28 days	305	Identical with gland removed at start of treatment
9	153	None	.....	5.0	For 7 days	161	Normal dioestrus gland; no lobule formation

* All animals were castrated at start of treatment except rat 9.

an abnormal gland with short widened ducts, irregular proliferation of end-buds and cyst formation. The lactogenic substance in this instance has still further stimulated secretory activity and has resulted in a diffuse but irregular distention of the ducts and end-buds, which accentuates the abnormal picture.

COMMENT

These experiments serve to show that benign mammary lesions can be induced in the rat by subjecting the animal to various abnormal endocrine influences. The actual mechanism by which these changes are brought about is probably a complex one, the administered substances acting to upset a normal endocrine balance and to effect abnormal changes in the tissue indirectly. It cannot be maintained that the injected principle is the specific cause of the abnormality; it is more probable that the excessive hormonal action is effected, in part at least, through the animal's own endocrine system.

These abnormal changes are histologically very similar to certain diseases of the human breast, and it is interesting to make a comparison when one is studying human material. However, it must be emphasized that there is no proof that a correlation exists between these mammary changes in the rat and those seen in the human being, and these experiments in no way prove that the mechanisms involved are the same. One can only say that a comparison makes it appear probable that these benign lesions of the human breast are in part of endocrine origin. In addition to other variations due to difference in species, the human mammary gland differs from those of all other species in its dense and abundant fibrous stroma. To this unique structure the human breast owes its external form, and it is this tissue which enters into the formation of many of the benign tumors of the breast. Because of this marked difference between the mammary gland of the human being and that of the experimental animal, little profitable correlation can be made between the changes in connective tissue observed in animals and those seen in human beings. It is probable, however, that in the rat and in the human being the loose areolar periductal connective tissue makes a similar response, while the dense stroma of the human breast has no counterpart in the rat, its place being taken by the loose fatty tissue into which the mammary tree of the rat ramifies.

SUMMARY AND CONCLUSIONS

A study has been made of mammary abnormalities in the rat resulting from the administration of a variety of endocrine substances, including estrogen, testosterone, progesterone and anterior pituitary substances. A comparison between these pathologic states and similar diseases of the human breast has been attempted. The following observations and conclusions may be made:

1. There is a distinct variation in histologic picture and in physiologic response in different portions of the mammary gland. These histologic differences are accentuated by growth stimuli and contribute to the pathologic picture of induced mammary lesions.

2. The mammary glands of males and females differ in their structure and in their inherent ability to respond to stimuli. These differences are entirely independent of the testis or ovary, as shown by early castration, and are therefore classed as genetic sexual differences.

3. These variations in different glands and in different portions of the same gland show that a large part of any pathologic mammary state has its origin in the gland itself and is independent of abnormal endocrine influences.

4. Administration of large doses of estrogen to rats for varying periods results in a variety of changes which simulate that group of

diseases of the human breast included in the term chronic mastitis. These abnormalities appear to be related to an endocrine disturbance in both the human being and the rat, and in the case of the rat the changes are the invariable result of high doses of estrogen.

5. The tendency for cyst formation, dilatation of ducts, epithelial proliferation and increase in periductal connective tissue to follow high or prolonged doses of estrogen, combined with the variation in response of different areas of the same mammary gland, results in a histologic picture which closely resembles that of chronic cystic mastitis in the human being.

6. When the changes of pregnancy in the breasts of rats are maintained by gonadotropic substances, prolonged periods of administration of high doses of estrogen fail to produce cystic changes. Similar beneficial effects on the chronic cystic mastitis of pregnancy and of lactation are noted in the human being.

7. Changes in the connective tissue of the rat are not analogous to changes in the stroma of the human breast; the periductal connective tissue alone appears to behave in a similar manner in the two species. Thus a study of the mammary hypertrophies and growths of fibrous tissue which involve this stroma in the human breast has not been possible with the rat.

8. The role of the pituitary lactogenic substance in influencing mammary histology is in need of further study. At present one can attribute to this substance only those secretory changes which may accompany the injection of other endocrine substances in animals with an intact pituitary gland.

9. The hormone of the corpus luteum, as represented by synthetic progesterone, has no influence on the structure of the rat's mammary gland.

10. A study of the changes in the breast at puberty in the male rat indicates that the maturing testis may be responsible for the mammary hypertrophy of boys at puberty, although in certain cases gynecomastia is probably the result of estrogenic stimulation. In other cases of gynecomastia, such as those in which involvement is purely unilateral, the condition must still be attributed to some inherent factor in the gland itself independent of an endocrine abnormality.

E. R. Squibb & Sons furnished estrogenic substance and lactogenic substance (prolactin); the Ciba Company furnished testosterone (perandren), and the Schering Corporation supplied progesterone (proluton).

INGUINAL HERNIOPLASTY WITH FASCIA TRANSPLANT

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Herniorrhaphy of any type has been found in all clinics to be an inadequate procedure for the treatment of some inguinal hernias. Recognition of this fact has led the most recent workers on this particular problem to seek some method that will effect a larger percentage of cures. Resulting methods in almost every instance comprise the use of fascia either as a suture material or for plication in the abdominal structures or in the form of a transplant.

In a search for reasons for recurrent or postoperative inguinal hernia, it is well to recall some anatomic conditions of the inguinal region. An indirect inguinal hernia has its exit from the abdominal cavity through the internal ring—an opening in the transversalis fascia. A direct inguinal hernia protrudes through the floor of the canal or else bulges this structure. It then becomes the first covering of such a hernia. All inguinal hernias, therefore, either pass through or push before them the transversalis fascia. These facts need emphasis. The transversalis fascia should be considered the first line of defense in the repair of an inguinal hernia. It is similar to fascia found elsewhere in the body, though it is thinner than other such tissue in the inguinal region. Fibrous tissue is known to be the best tissue for the application of a transplant of fascia, but its importance in this respect has not been generally recognized.

The spermatic cord in the inguinal region is in direct contact with the transversalis fascia and is attached to it by the fibers of the cremaster muscle. These fibers must be freed and retracted with the cord for complete exposure of the floor of the inguinal canal. This procedure is also necessary to repair the internal inguinal ring completely. Any method of herniorrhaphy, therefore, that does not include mobilization of the spermatic cord cannot allow effective repair of the internal ring or repair and reenforcement of the floor of the canal.

Inguinal hernia of the congenital type, such as is found in children and some adults, may be repaired successfully by high ligation of the sac, transplantation of the stump and suture of the internal oblique muscle to the fascia reflected from Poupart's ligament.

From the Surgical Department, Division B, of the Jefferson Hospital.

Since inguinal hernia cannot recur or a new hernia of another type develop in the inguinal canal without forcing an exit through the internal ring or the transversalis fascia as the floor of the canal, it is entirely reasonable to state that recurrent or new hernia will occur less frequently when this structure is properly *repaired* and *reenforced*. Such a statement in no wise indicates that these procedures constitute a complete operation for the cure of inguinal hernia. They are, however, definitely indicated in the following: (1) all direct inguinal hernias; (2) indirect inguinal hernia, when the internal ring is large and the transversalis fascia poorly developed or bulging; (3) inguinal hernia with a double or saddle-bag sac; (4) indirect hernia, when the internal oblique muscle and conjoined tendon are found to be congenitally deficient, atrophied or largely replaced by fat; (5) indirect hernia in adults whose occupation requires heavy lifting or other physical activity that tends to greatly increase intra-abdominal pressure, and (6) recurrent or postoperative inguinal hernia.

Repair of direct hernia by using only the tissues of the abdominal wall in the inguinal region has resulted in recurrent or postoperative inguinal hernia in from 10 to 32 per cent of the reported cases. Repair of recurrent hernia by such methods has resulted in recurrence in 40 per cent of the cases in surgical division B at the Jefferson Hospital.

Various methods have been devised in which strips of fascia or transplants have been utilized. It is without the scope of this paper to describe all such methods, but some information of the development of repair with fascia is given.

TRANSPLANTATION OF FASCIA

The first use of a transplant of fascia in the repair of hernia is attributed to Kirschner [1] in 1910. He reported forty successful operations in which he used a free flap of fascia lata secured by separate incisions in the thigh and sutured ventral to the conjoined tendon. No experimental work had preceded these operations, but Davis [2] in 1911, by animal experimentation, found that a transplant of fascia unites firmly with the edges of the muscles and parietal peritoneum and that visceral peritoneum coming in contact with such a flap does not adhere. Later experimental work reported by Lewis and Davis [3] revealed that a transplant of fascia subcutaneously placed and left unattached remains viable but that it contracts and thickens. The experimental work of Von

1. Kirschner, M.: Die praktischen Ergebnisse der freien Fascientransplantation, Arch. f. klin. Chir. **92**:888-912, 1910.

2. Davis, J. S.: The Transplantation of Free Flaps of Fascia, Bull. Johns Hopkins Hosp. **22**:372-381, 1911.

3. Lewis, D. D., and Davis, C. B.: Repair of Tendons by Fascia Transplantation, J. A. M. A. **62**:602-604 (Feb. 21) 1914.

Eberts and Hill,[4] reported in 1914, demonstrated that the smooth external surface of a transplant of fascia heals best when sutured closely in contact with other tissues. Such a flap, therefore, should be so turned that the surface of the muscle is outward. They found that a free flap of fascia when sutured heals without reaction or diminution in size. They furthermore pointed out that gentle handling of tissues and strict asepsis must be practiced in order to get such results.

Gallie and LeMesurier[5] in 1921, from animal experimentation, found that the edges of incised fascia heal by means of cells from the attached areolar tissue. Such healing is not firm. This prompted them to practice and recommend the removal of all areolar tissue and the scarification of muscle and the overlapping of fascia in repair. These investigators later found that a fascial suture becomes a permanent part of the tissue in which it is used. Other experimental work done on animals by Koontz,[6] and first reported in 1926, demonstrated that fascia lata and inguinal ligament, if cleaned of all areolar tissue and coapted, unites firmly by the growing together of the connective tissue fibers of each. The strength of such healing was found to depend on the intimacy of contact of the fibrous components and was referred to as fascia to fascia healing. Koontz therefore recommended tight sutures in transplantation of fascia. Other work with such transplants or sutures has been in the repair of hernia in man.

Thus one finds ample experimental evidence to prove that a transplant of fascia heals firmly when freed of all areolar tissue and fat and completely severed from its blood supply, provided it is closely and firmly sutured under strict aseptic conditions with the smooth surface in contact. Scarification of muscle before suturing results in firmer union with fascia, and surgeons of experience do not hesitate to accept this experimental finding, for they are aware that it is in keeping with clinical results.

HERNIOPLASTY

Mann[7] reported the use of transplants in the repair of hernia. His method, similar to that of Kirschner, consists of the application of the transplant ventral to the internal oblique muscle. He recommended suturing such a flap slightly "on a stretch," though reasons for this have not been demonstrated experimentally.

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4. Von Eberts, E. M., and Hill, W. H. P.: Free Transplantation of Fascia, Surg., Gynec. & Obst. **18**:318-321, 1914.

5. Gallie, W. E., and LeMesurier, A. B.: The Use of Living Sutures in Operative Surgery, Canad. M. A. J. **11**:504-513, 1921.

6. Koontz, A. R.: Experimental Results in the Use of Dead Fascia Grafts for Hernia Repair, Ann. Surg. **83**:523-536, 1926.

7. Mann, A. T.: New Methods of Operating for Difficult Herniae, Journal-Lancet **37**:331-337, 1917.

McArthur,[8] Mackechnie,[9] Harrison,[10] McEachern,[11] Adair,[12] Darling,[13] Cowell [14] and, most recently, Turner [15] reported the use of sutures of fascia or of some method of transplantation of fascia in the repair of inguinal hernia. Cowell's method consists of the use of strips of fascia of the external oblique muscle. These strips are attached at one end and are used as sutures to coapt the structures of the abdominal wall. Large-eyed needles made especially for this purpose are used, and it is necessary to tie the sutures of fascia in the needles. Cowell refuses no one operation and has reported excellent results, even in patients from 60 to 80 years of age.

A method of hernioplasty which marks a definite advancement was devised by Turner of Guy's Hospital in London. He turns up a pedicle flap of fascia from the anterior surface of the thigh. This is made to pass through the inguinal ligament to which its base is attached and is sutured to the floor of the inguinal canal. This technic was used in his clinics on sixty-five patients, all of whom were considered to have hernias which were inoperable by the usual method. Of twenty-five of those who were examined later, two were found to have hernia. One hernia was of the same type as was present before operation, and the other was a hernia of a type other than the primary hernia and was classified as a postoperative inguinal hernia.

These notes and descriptions of methods devised by others are of necessity brief in this presentation. They will serve, however, to indicate some steps in the development of inguinal hernioplasty. I trust that they will also assist in the recognition of the advantages in the operation about to be described.

THE AUTHOR'S OPERATION

An incision is made through the skin and subcutaneous tissue from a point just medial and cephalic to the anterior superior spine of the ilium. It is curved convexly downward and ends cephalic to the spine of the pubis. It should not

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8. McArthur, L. L.: Autoplastic Sutures in Hernia and Other Diastases, J. A. M. A. **43**:1039-1048 (Oct. 8) 1904.

9. Mackechnie, H. N.: Bilateral Direct Inguinal Hernia, Internat. Clin. **2**: 29-33, 1922.

10. Harrison, P. W.: Inguinal Hernia: A Study of the Principles Involved in the Surgical Treatment, Arch. Surg. **4**:680-689 (May) 1922.

11. McEachern, J. D.: Method of Repairing Inguinal Hernia with Living Sutures Taken from External Oblique Tendon, Ann. Surg. **79**:758-761, 1924.

12. Adair, F. L.: Aponeurosis of External Oblique as Source of Living Sutures for Inguinal Herniotomy, J. A. M. A. **82**:629-630 (Feb. 23) 1924.

13. Darling, H. C. R.: Recurrent Inguinal Hernia: Its Causation and Prevention, M. J. Australia **2**:151-158, 1927.

14. Cowell, E. M.: Hernia and Hernioplasty, London, H. K. Lewis & Company, 1927.

15. Turner, Philip: Hernioplasty, Guy's Hosp. Rep. **83**:233-251, 1933.

cross the crease of skin in the groin. The flap of skin and subcutaneous tissue is reflected upward, exposing the aponeurosis of the external oblique muscle, which is incised ventral to the spermatic cord. This incision is prolonged laterally beyond the internal ring and medially through the external ring. The aponeurosis is separated from the underlying structures and freed of fat and areolar tissue by the use of dry gauze. The fibers of the cremaster muscle are separated with blunt scissors when an indirect hernia is being repaired. The sac is located, isolated and opened. High ligation is done with a transfixing suture, and at least a part of the excess sac is plicated and made to fit snugly around the cord dorsal to the internal oblique muscle and cephalic to the internal ring. It is sutured in this position. Double sacs are sought and, when found, are converted into one sac. The spermatic cord with the cremaster muscle is freed from the inguinal ligament and the transversalis fascia. All fibers of this muscle, fat and areolar tissue are removed from this fascia. In the operation for direct hernia the sac is opened, its edges are sutured from within and overlapped and may be transplanted under the internal oblique muscle or allowed to retract in the abdomen. The transversalis fascia is sutured so that its edges and the sac are buried. Overlapping of the transversalis fascia necessitates complete removal of fat and areolar tissue from its under-surface if firm union is to result. Since this is a rather difficult technical procedure, suture by inverting the edges is practiced. The internal ring is snugly sutured so as barely to emit the cord without interfering with its circulation. To accomplish this, the internal oblique muscle must be retracted rather severely. The lower flap of skin and subcutaneous tissue is freed laterally from the fascia covering the muscles of the thigh and retracted. Exposure may be increased by extending this incision cephalically. A transplant of sufficient size to cover the inguinal floor is removed from the fascia lata just caudad and somewhat dorsal to the anterior pubic spine. Bleeding vessels are carefully clamped and ligated, and a gauze sponge is placed there to control oozing. The corners of the transplant are picked up with small hemostats, carefully freed of fat and areolar tissue, inverted and sutured to the transversalis fascia with a continuous suture of no. 00 chromic catgut. This part of the operation requires careful technic, but by first suturing the corners of the transplant, the procedure is facilitated. A few firmly tied single stitches are used for close coaptation. The lateral corners of this flap are sutured above and below the cord. These sutures coapt the transplant with the internal ring, which procedure is particularly important when a large indirect hernia is being repaired.

The operation is continued by suturing the conjoined tendon and internal oblique muscle to the inguinal ligament with interrupted sutures of no. 1 chromic catgut. These sutures are so placed that the muscular fibers are not separated.

If there is marked deficiency of the conjoined tendon, a triangular flap from the sheath of the rectus muscle is turned down and sutured to the underlying structures.

The flaps of the fascia of the external oblique muscle are overlapped slightly and sutured dorsal to the cord. Gauze is removed from the exposed area of the thigh, which is carefully inspected for bleeding. Strict hemostasis in this area is very important. The skin flaps are closed without drainage with nonabsorbable sutures. Dressings are secured by long strips of adhesive tape so placed as to give pressure over the part of the thigh from which the transplant was taken. A separate incision below the iliac spine, for the purpose of securing a suitable transplant of fascia, is rarely necessary.

The following details in technic are important: careful preparation of the skin, strict asepsis, strict hemostasis and removal of all fat and areolar tissue from

the tissues used in repair. All sutures are tied tightly, but undue tension of the tissues is avoided. The exit of the cord through the fascia of the external oblique muscle is made medial to the internal ring. The sutures which fix the cephalic margin of the fascial transplant must not include fibers of the internal oblique muscle or conjoined tendon, for these must be free for suture to the inguinal ligament. The iliohypogastric and ilio-inguinal nerves are recognized, preserved intact and not included in the sutures. This care prevents after-pain and helps preserve tone and prevent atrophy of the tissues which they supply.

This operation sacrifices none of the advantages of the best methods of herniorrhaphy.

RESULTS

Forty-four hernias have been repaired by this method. Each of these was selected because it belonged to one of the groups in which the transplantation of fascia is definitely indicated. Twenty of this group were of the indirect type, eleven were either direct or hernias with saddle-bag sacs and six were recurrent hernias. One of the latter had been repaired previously, and another had been repaired twice. Thirty-seven of the patients in this series have been examined in the follow-up clinic. Nineteen were examined from twelve to twenty-four months after operation; fourteen, from five to twelve months, and four, from two to four months. The number of patients in the various age groups follow: from 70 to 80 years, one; from 60 to 70, three; from 50 to 60, five; from 40 to 50, nine; from 30 to 40, eight; from 20 to 30, six, and from 15 to 20, five.

No recurrent or postoperative hernia has developed when the operation was done successfully. There have been, however, four cases in which the operation was a failure due to hemorrhage or infection and sloughing of the transplant. The cases in which failure occurred are reported here:

CASE 1.—C. N., aged 49, twenty-one years previously had undergone bilateral herniorrhaphy. He was admitted to the hospital for operation for bilateral recurrent direct hernia. Infiltration anesthesia was used, and both hernias were repaired, with a period of eleven days between operations. At operation the conjoined tendon and internal oblique muscles were found to be atrophied, and the transversalis fascia was unusually thin. Some fat was excised from the floor of the canal, and the fascia was repaired. A hematoma developed in the thigh where the transplant of fascia was removed. Infection followed in the site of the inguinal repair. Hernia developed almost immediately after operation, and thirty days after the first hernioplasty reoperation was done, the same method being used. Eight months after the second operation, careful examination revealed firm tissues in the inguinal region—an excellent result. The failure of the first repair must be attributed to infection.

CASE 2.—C. C., aged 53, was admitted to the hospital with bilateral inguinal hernia. The left was a saddle-bag, or double, hernia. It was repaired with the patient under ether anesthesia by the method described herein. A part of the sac was excised, and considerable fat was removed from underneath the transversalis fascia—the floor of the canal. On the fifth postoperative day the patient had a chill and a temperature of 104.2 F.; the following day another chill occurred with

a temperature of 102.2 F. Physical examination gave entirely negative results, save for some mild reaction in the wound. I believe that there was infection of the transplant, which resulted in its destruction rather than in the formation of an abscess. Six months after operation a postoperative direct hernia was discovered on examination. The recurrence is attributed to infection.

CASE 3.—M. M., aged 22, was admitted to the hospital for repair of a large indirect inguinal hernia. Operation was carried out with the patient under ether anesthesia. The tissues were fairly well developed. A large hematoma appeared in the thigh and in the inguinal region a few hours after operation. The incision in the skin was opened, and some clots were removed daily for several days. I believe that the transplant was absorbed or else lost with some of the clots. The patient returned to work five weeks after discharge. Postoperative hernia of the direct type was found on examination four months later. This case was one of the earliest in which this operation was used, and recurrence is attributed to hemorrhage resulting from poor technic.

CASE 4.—M. K., aged 48, had bilateral indirect inguinal hernia, the right hernia being in the scrotum. Operation was done with the patient under ether anesthesia, and a saddle-bag sac was found. The internal oblique muscle was so markedly atrophied that it was of little use in repair. The internal ring was very large. Pulmonary complications developed postoperatively and also an infection of the operative wound, which resulted in the formation of an abscess and sloughing of the transplant. The patient returned to work as a janitor as soon as he was discharged from the hospital. A postoperative hernia of the indirect type resulted about ten months later.

CONCLUSIONS

The tissues in the inguinal region are inadequate for the repair of hernia in some patients.

The transversalis fascia should be considered the first line of defense in repair.

Mobilization of the cord is necessary for repair of the transversalis fascia, particularly of the internal ring.

The floor of the inguinal canal (transversalis fascia) is the best place for the application of a transplant of fascia.

Fascia for transplantation may be taken from the fascia lata through an incision made for repair of the hernia.

Strict asepsis and careful hemostasis are most important in the transplantation of fascia. Infection and hemorrhage were the causes of the failures in the reported cases.

This series of cases represents the group of inguinal hernias in which the incidence of recurrence is highest.

SIXTY-FIFTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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DEFORMITIES IN DEVELOPMENT

Generalized Osteochondrodystrophy.—In an attempt to secure a better classification of chondrodystrophies and osteochondrodystrophies, Hirsch [1] quotes the classification suggested by Jaffe. The latter coins a new term, "eccentrochondroplasia," since the epiphysis in this condition develops not from a central nucleus but from multiple eccentric centers of ossification, as shown in roentgenograms. There are three stages in this disease: a latent stage, a florid stage and a stage of healing with its aftermath of deformity. Though the condition is not generally recognized until the child begins to walk, roentgenographic signs become apparent with the onset of ossification of the epiphysial cartilages. The visible signs of this condition are: thoracic kyphosis with prominence of the sternum, forward tipping of the pelvis, genu valgum and flat and everted feet. The roentgenographic signs are chiefly epiphysial changes associated with a malacia which produces a deformity in the size and shape of both the shafts and the articulating ends of the bone.

This report of progress is obtained from a review of 123 papers selected from 194 titles relating to orthopedic surgery and appearing in medical publications approximately between July 3 and Nov. 1, 1937.

1. Hirsch, I. S.: J. Bone & Joint Surg. **19**:297, 1937.

In the florid stage the zones of ossification of all the bones, including the vertebrae but excepting the flat bones of the skull, show an increase in width in the cartilage plates. The cartilage does not show the normal regularly progressive zone of ossification, but instead its advance is irregular and disorderly, with uneven lines being left behind in the epiphyses and diaphysis. Small nuclei of bone are seen distributed through the cartilage. As growth proceeds, these points coalesce, giving the main nucleus a ragged contour. The malacic changes result in humerus varus, coxa vara and genu valgum. On the concave side the periosteum is thickened with the formation of osteophytes; on the convex side the cortex is thin. The vertebral bodies are flattened, and the anterior margins are pointed or tongue shaped along the inferior border. The kyphosis is usually due to wedging between the lower two thoracic vertebrae. The sacral segments usually remain unfused. In the stage of healing there is consolidation of the irregular islands of ossification, but the shape is never completely normal. The ends of the long and short bones are enlarged and flattened. Roentgenologic examination of the hips reveals small femoral heads with short necks in coxa vara in relatively large acetabulums. The vertebrae are platelloid.

POLIOMYELITIS

Immunity and Portal of Entry in Poliomyelitis.—Toomey [2] discusses the confusing and complicated reports on experimental immunization against poliomyelitis. He believes that neutralizing antibodies (humoral) are a good index of immunity. Contrary opinions, he believes, are due to the fact that experimentally the disease is not introduced through the natural portal of entry. He believes that the natural portal is the gastrointestinal tract and that the virus is absorbed there and spreads along the sympathetic and parasympathetic chains to the lumbar, cervical or bulbar area. The usual spread, he believes, may be prevented by free cholesterol in the intestine or even by cholesterol in the white nerve fibers.

CHRONIC ARTHRITIS

Fever Therapy for Arthritis.—Simmons and his co-workers [3] studied the value of fever therapy for the arthritides, using the Kettering hypertherm in 81 cases. In 23 cases of gonorrheal arthritis 82 per cent of the patients were cured or markedly improved after twenty-six hours of fever with a temperature between 106 and 107 F. They believe that a minimum of twenty-five hours of fever is necessary before one con-

2. Toomey, J. A.: Active and Passive Immunity and Portal of Entry in Poliomyelitis, J. A. M. A. **109**:402 (Aug. 7) 1937.

3. Simmons, E. E.: Am. J. M. Sc. **194**:170, 1937.

cludes that this form of treatment of gonorrheal arthritis is a failure. Of 36 patients with atrophic arthritis, 78 per cent were benefited by a temperature around 103 to 104 F. In 10 cases of hypertrophic arthritis the treatment seemed to help only patients with a superimposed infectious or traumatic element. Nine of 12 patients with acute rheumatic fever showed improvement. With the exception of the bactericidal effect in gonorrheal arthritis, they conclude that the beneficial result is probably due to vasodilatation and increased immunologic response.

Gonorrheal Arthritis.—Keefer and Spink [4] gave a detailed discussion of gonorrheal arthritis based on a study of 140 patients. They review the clinical features of the disease, emphasizing associated lesions, such as tenosynovitis. Pathologic examination showed ankylosis to be fibrous and rarely bony. Organisms were recovered from the joints in 26 cases. Complement fixation tests gave a positive reaction in 86 per cent of the specimens of blood examined and in 66 per cent of the synovial fluids. Generally accepted methods of treatment are discussed. (Sulfanilamide has been used in 3 patients only.)

Care of Feet in Chronic Arthritis.—Kuhns [5] emphasizes the frequency of involvement of the foot in arthritis and the disabling deformities that often result. Early treatment, consisting of complete rest during the acute stage of the disease, supplemented by physical therapy and exercises, prevented most of these. Proper shoes and adequate supports are essential when the patient begins to bear his weight, or deformity will occur. Neglected patients all showed deformities. If discovered early these could be corrected by conservative measures, such as strapping, application of corrective plasters and manipulations. A certain number of untreated conditions were too far advanced when first seen to be helped by other than operative procedures. The simplest and least traumatic forms of surgical intervention give the best results.

OSTEOMYELITIS

Nonspecific Osteitis of the Ribs.—Poulsson [6] reports 3 instances of metastatic nonspecific osteitis of the ribs observed in the Lund Hospital, Sweden. These followed minor infections in distant parts of the body in adults. In 1 case tissue secured by operation confirmed the diagnosis. Two patients had a small area of transverse destruction with spontaneous fracture, and the other had multiple areas of destruction in the ribs. Differential diagnosis from malignant conditions is best

4. Keefer, C. S., and Spink, W. W.: Gonococcic Arthritis: Pathogenesis, Mechanism of Recovery and Treatment, J. A. M. A. **109**:1448 (Oct. 30) 1937.

5. Kuhns, J. G.: Care of the Feet in Chronic Arthritis, J. A. M. A. **109**:1108 (Oct. 2) 1937.

6. Poulsson, K. T.: Acta radiol. **18**:642, 1937.

made by repeatedly making roentgenograms, which show a marked tendency to spontaneous healing in this form of osteitis.

[ED. NOTE.—If there is any question of neoplastic metastases it is often better to perform a biopsy than to wait for roentgenologic evidence of changes.]

Infection of the Spinal Epidural Space.—Browder and Meyers [7] present 7 case histories of spinal epidural infection and discuss this clinical entity. They believe that it is frequently missed clinically and the osteomyelitic involvement of the vertebrae overlooked at autopsy. The condition was acute in 5 of their cases and chronic in 2. Clinically the patients with acute attacks give a history of previous infection, boring pain in the spine, radicular pain and involvement of the spinal cord. When the infection is chronic the syndrome is not so definite, although these same features, to a less degree, usually occur. They believe that the condition comes from an infection adjacent to the vertebral column or by a hematogenous route from a more remotely situated focus, such as acute infection of the upper part of the respiratory tract, otitis media, tonsillitis, furunculosis, phlebitis, puerperal sepsis or infection of the urinary tract. Infections of the latter type are characterized by a zone of metastatic vertebral osteomyelitis. The cases reported presented, besides the spinal epidural infection, 2 instances of osteomyelitis in the cervical region, 2 in the dorsal region, 1 in the lumbar region, 1 in the head of the sixth rib and 1 in an unknown site.

Disturbance of Growth Resulting from Osteomyelitis.—Siegling [8] reviews 423 cases of osteomyelitis seen at the University of Chicago Clinics. Two hundred and forty-one of these were instances of involvement of the long bones in children. In 4.9 per cent there was increase in the length of the long bones, and in 31.5 per cent there was an arrest of growth; included in this group were 79 instances of suppurative arthritis of the hip joint. The author warns against trauma to the epiphysis in operative procedures for osteomyelitis, stressing particularly that the periosteum should not be stripped from the cartilage near the epiphysis. Parents whose children have had osteomyelitis of the long bones should be warned of the frequent occurrence of deformity.

Osteomyelitis of the Long Bones and Typhoid Fever.—Moiroud [9] reviews the history of typhoid osteomyelitis. Osseous lesions following recovery from typhoid fever have been commonly observed. In a large number of cases staphylococci have been obtained from clinical speci-

7. Browder, G., and Meyers, R.: Am. J. Surg. **37**:4, 1937.
8. Siegling, J. A.: Illinois M. J. **72**:422, 1937.
9. Moiroud, P.: Presse méd. **45**:980, 1937.

mens instead of Bacillus typhosus. The author gives a number of differentiating signs. In typhoid osteomyelitis the local symptoms are less acute than in staphylococcic infections. There is detachment of the periosteum; there may be lamellar sequestrums. Typhoid osteomyelitis is cured usually by simple surgical intervention. When the staphylococcus is the infecting organism, there are more extensive osseous hypertrophy and destruction of the bone, and simple intervention rarely cures. A case of typhoid fever with osteomyelitis in which specimens yielded the staphylococcus is reported in detail.

Osteomyelitis and Osteitis Paratyphosa.—Just [10] reports that in an epidemic of paratyphoid fever at Innsbruck, Austria, in which 152 persons had the disease, there was a case in which osteomyelitis developed one year later in the ulna of an 18 year old girl. Bacillus paratyphosus was recovered at operation. Histologic examination showed sclerosing osteitis. The arm healed after operation. The author reviews the literature, which supports his own belief that this was a rare complication in paratyphoid fever.

TUBERCULOSIS

Tuberculous Perichondritis and Periostitis of the Ribs.—During fifteen years, study of 50 cases of typhoid and paratyphoid chondromyelitis showed occasional tuberculous perichondritis. From 1921 to 1933, 14 patients in whose cases the diagnosis was definitely determined came under observation. From this study Chaklin [11] observed that in typhoid chondromyelitis the cartilage and marrow are primarily affected, with destruction proceeding from the center to the periphery, whereas in tuberculous perichondritis the destruction usually begins in the periphery and extends inward. Radical removal of tuberculous ribs and cartilages gives the most favorable results up to the time when an abscess forms. If the lesion involves only the bony part of the rib, it is possible to limit the resection, and injury to the cartilage is thus avoided. When an abscess or a fistula is present, conservative treatment is indicated. Photographs and roentgenograms of pathologic specimens are given.

Tuberculous Foci Near Joints.—An analysis of 33 patients treated conservatively and 33 treated by surgical excision enables Nase [12] to give indications for the treatment of tuberculous foci. One half to two thirds of all tuberculous lesions ruptured from a bony focus into the neighboring joint. The surgical problem is to minimize this involvement of the joint. The patients of the series were followed for vary-

10. Just, E.: Deutsche Ztschr. f. Chir. **249**:105, 1937.
11. Chaklin, V. D.: J. Bone & Joint Surg. **19**:395, 1937.
12. Nase, H.: Beitr. z. klin. Chir. **165**:572, 1937.

ing periods, ranging from five to fifteen years. In general, conservative therapy, when successful, brought about healing in an average of fifteen months, the author states. Fistula or abscess developed in 45 per cent of the cases. Of 17 cases of lesions in the long bone treated by surgical extirpation of the focus, in 12 there was healing. The time required for healing in the surgically treated patients averaged seven months. Individual cases are analyzed. In general, if the local tuberculous lesions are in the short bones of the extremities, if they are inaccessible to surgical intervention or if they threaten epiphysial damage to children, they had best be treated conservatively. Conservative therapy is also advised in dubious cases of lesions in the upper extremities, since strains of weight bearing do not exist here. However, operative therapy is advised in the long bones and in the neighborhood of the longer joints, at all ages, as the procedure of choice. Local excision of the focus helps the general resistance in cases in which generalized infection exists.

[ED. NOTE.—Attempts to remove tuberculous foci from the long bones in the past have frequently resulted in deformity and disturbance in growth.]

Kushizaki and Saito [13] report 2 cases of primary muscular tuberculosis, one in a 24 year old man and the other in a 34 year old woman. In the first the lesion was solitary, involving the pectoralis major muscle; in the second case multiple almost symmetrical masses were present in the four extremities. This case presented also calcified hilar nodes. The first patient had no other discernible tuberculous lesions. The masses are difficult to diagnose clinically, since they move with the muscle and are smooth and usually tender. The overlying skin is not involved. Radical excision is advised. Pathologic identification usually is essential to diagnosis, since the masses grossly resemble tumors, parasitic infestation or chronic inflammatory lesions. The more recent literature is carefully analyzed. Colored plates of the operative observations in the 2 cases are reproduced.

INVOLVEMENT OF THE BACK

Surgical Treatment of Pain Low in the Back.—Ghormley and Wesson [14] present a review of all cases in which patients were subjected to fusion operations at the Mayo Clinic for low spinal and sciatic pain. Operation is advised, after a study to exclude the possibility of neurologic disturbances in patients from 20 to 50 years of age. In this series of 155 cases the average duration of symptoms was five and a half years. The group in which pain of static origin is relieved by rest

13. Kushizaki, S., and Saito, K.: Beitr. z. klin. Chir. **165**:177, 1937.
14. Ghormley, R. K., and Wesson, H. R.: South. M. J. **30**:806, 1937.

with or without traction offers the best prognosis after fusion. Fasciotomies and herniated intervertebral disks are not included in this series. Several types of operative procedure were used: (1) lumbosacral fusion with iliac or tibial grafts; (2) lumbosacral fusion with excision of an articular facet, and (3) lumbosacral fusion combined with sacroiliac fusion. In the tables included in this article it is clearly demonstrated that cases for fusion are not easily chosen nor are the results uniformly good. The patients with the highest percentage of "good" results (72 per cent) were those on whom a lumbosacral graft from the iliac crest with a Smith-Petersen type of sacroiliac fusion was done. Sacroiliac fusions alone yielded at best 58 per cent good results. Resections of sacralized transverse processes, an operation done in the earlier series, yielded only 29 per cent good results. The authors stress the fact that lumbosacral and sacroiliac fusion should not be done as a last resort unless the symptoms are relieved by rest in bed and traction.

[ED. NOTE.—This article presents an unbiased point of view with careful analysis of the end results. Indiscriminate operations involving spinal fusion should go the way of all "cure-all" types of operative procedure.]

Hypertrophy of the Ligamentum Flavum.—Seven cases in which pain low in the back was produced by hypertrophy of the ligamentum flavum are reported by Spurling and his associates.[15] The predominant complaint was pain low in the back, radiating into one lower extremity in 6 cases and into both lower extremities in 1 case. Tenderness over the spine was constant, as were sensory changes. Regional reflexes of the tendons were altered in all but 1 case. Diagnosis depended first on a careful neurologic examination and second on injection of iodized oil into the spinal canal by means of a lumbar puncture. Lumbar punctures gave no diagnostic results except that there was elevation of the total protein content of the fluid from 45 to 175 mg. per hundred cubic centimeters. Two cubic centimeters of iodized oil was sufficient to show the lesion on the tilting table. Treatment consisted of removal of the thickened ligament. In all cases the ligament involved ran between the fourth and the fifth lumbar vertebra, and in 6 cases the laminae of the fourth lumbar vertebra were enlarged. Normal and pathologic anatomic structure is discussed in detail. The results of operation were good, although no patient has been followed more than eight months.

Diseases Affecting the Intervertebral Foramens.—Oppenheimer [16] discusses the roentgenologic observations in cases in which there are

15. Spurling, R. G.; Mayfield, F. H., and Rogers, J. B.: Hypertrophy of Ligamenta Flava as Cause of Low Back Pain, J. A. M. A. **109**:928 (Sept. 18) 1937.

16. Oppenheimer, A.: Radiology **28**:582, 1937.

symptoms of segmental neuritis which may be attributed to compression of nerves within the intervertebral foramens. Attention is called to two mechanisms by which this compression is brought about, namely, (1) collapse of the walls of the foramens and (2) constriction of the lumens of the foramens. Under the first heading is described thinning of the intervertebral disks (discogenetic disease), arising from various causes, which produces collapse of the anterior half of the foramen, followed by anterior subluxation of the superior articular process of the subjacent vertebra. This condition is often associated with the exostoses typical of hypertrophic spondylitis. Under the second heading is described primary arthritis of the apophysial joints, which may result in ankylosis of the articular facets, the constriction of the foramen being due to periarticular swelling or later to the ossification of synovial membranes. Collapse results mainly from thinning of the disk; hence it begins at the anterior margin of the foramen. Constriction results from inflammation of the synovial membranes of the apophysial joints and therefore begins at the posterior margin. Roentgenograms illustrating the conditions described are presented.

Injuries to the Accessory Processes of the Vertebrae.—Mensor [17] stresses the importance of injuries to the spine which involve torsion. Roentgenologic studies of 141 patients who gave a history of such injuries revealed that 22 had fractures involving the accessory processes. Nine of these also had anomalies involving the lamina, pedicle or articular facets. The ratio of frequency of fractures to anomalies was 2½ to 1. Particular attention is called to the necessity of taking roentgenograms at various angles to show the fractures and anomalies. Excellent reproductions of roentgenograms illustrating the text together with line drawings are included.

Painful Coccyx.—In a study of 278 cases of painful coccyx, Duncan [18] observed that in 89 per cent symptoms were preceded by an injury to the coccyx, which usually consisted of a fall in the sitting position. Hence he concludes that coccygodynia is due to a local injury and only rarely is of psychic origin. Ninety-seven per cent of his patients were women. He believes that this large proportion is explained by the more prominent posterior position of the coccyx in women, which makes it more liable to injury. Roentgenologic studies of patients with and without coccygodynia showed that almost any variation except fracture or dislocation was of equal occurrence in the sexes. Conservative treatment, consisting of postural exercises, exercises causing the soft tissues surrounding the coccyx to act as a natural cushion, hot sitz baths, laxatives and local massage is recommended for

17. Mensor, M. C.: J. Bone & Joint Surg. **19**:381, 1937.

18. Duncan, G. A.: Painful Coccyx, Arch. Surg. **34**:1088 (June) 1937.

a period up to six months. Dislocation of the coccyx, however, may be manipulated and reduced under anesthesia in the early stage. If nonoperative measures fail to give relief, coccygectomy is then advised. Thirty patients, or 11 per cent, had a resection of the coccyx. The average age was 32 years, and the average duration of symptoms before operation was eighteen months. The patients were followed for an average of two years. Seventy-four per cent were completely relieved of pain, 9 per cent partially helped and 17 per cent unimproved.

Skeletal Deformities After Empyema.—In an excellent article Bisgard [19] comes to the following conclusions: Thoracogenic scolioses are of two types, pleurogenic and thoracoplastogenic. Both are preventable and are curable if corrected in their incipiency. Pleurogenic deformities can be prevented by: (1) the prevention of the formation of a pleural scar by early cure of the empyema or pleuritis and (2) constant attention to the maintenance of straight alinement or preferably of an overcorrected position of the spine. This can be accomplished by means of (*a*) postural wedging, (*b*) placing the body in a corrective cast of plaster of paris or (*c*) resection of ribs on the side of the concavity. To facilitate correction and the use of corrective measures, it is helpful to anesthetize the area of the wound by crushing the intercostal nerves which supply the area. Extensive and rigid deformities of the spine and costal framework are incurable.

Lateral Curvature Following Thoracoplasty.—Cleveland [20] discusses the development of scoliosis with dorsal curve toward the side on which the operation was performed after thoracoplasty for pulmonary tuberculosis. This scoliosis is worse in children but may be present also in adults. The analogy is drawn between this type of scoliosis and paralytic scoliosis. A longer period of rest in bed after operation is advised. In many of the cases spinal fusion should be performed to prevent the advance of spinal deformity.

NEOPLASMS

Sclerosing Sarcoma of the Bone.—In a study of 158 cases of sclerosing sarcoma of the bone, Lewis and Geschickter [21] noted that the most characteristic location of the tumor is in the cancellous or cortical portion of the bone itself and not in the periosteal or subperiosteal region. The sunburst, or periosteal manifestation, seen in the roentgenogram is a late development. Because of the rapid growth of the tumor, this mode of onset is obscured. That the tumor may begin in the bone is indicated by cases in which the bulk of the tumor is confined

19. Bisgard, J. D.: J. Thoracic Surg. **6**:609, 1937.
20. Cleveland, M.: J. Thoracic Surg. **6**:595, 1937.
21. Lewis, D., and Geschickter, C. F.: Sclerosing Sarcoma of the Bone, Arch. Surg. **34**:1010 (June) 1937.

to the bone in relatively advanced stages. Histologically the tumor is composed of osseous and osteoid tissue. Malignant osteoblasts are separated by relatively large amounts of intercellular osteoid tissue. Spicules of bone and spindle cells representing undifferentiated connective tissue are also found. The tumor apparently arises from preosseous connective tissue and rapidly differentiates toward the end product, namely bone. Seventy-two, or about one half, of the tumors occurred in the lower end of the femur or the upper end of the tibia. Four developed in the skull, 10 in the upper or lower jaw, 3 in a vertebra, 4 in a bone on the pelvis and 4 in the scapula. Sclerosing sarcoma occurs most frequently in adolescents and in young adults. There were only 36 patients over 25 years of age. In approximately half of the cases trauma was mentioned in connection with the beginning of the tumor. In some cases there were fever, the patient's temperature being as high as 101 F., and leukocytosis, usually with a white cell count under 18,000. Clinically the swelling was firm, smooth and continuous with the bone. Palpation occasionally revealed crepitus. The diagnosis was made by roentgenologic and microscopic examination.

Roentgenologically the tumor appears to develop in the end of the bone on the side of the epiphysial line toward the shaft. The earliest evidence of the formation of the tumor is sclerosis with obliteration of the normal markings of the bones. The most strongly marked involvement of cancellous bone in the earliest stages is immediately adjacent to the epiphysial line. The earliest indication of periosteal reaction is spicules of bone laid down at right angles to the shaft. Clinically the tumor runs a relatively acute course, the symptoms rarely remaining more than six months. Pain, swelling and impairment of function appear in this order. One hundred and six patients were followed for more than five years or until a fatal termination. Of these, 18, or 17 per cent, were living at the end of the five year period. For all of the latter patients resection or amputation was employed. No five year cures followed irradiation. However, in cases of inoperable tumor in the bones of the pelvis or femur in which pulmonary metastases had occurred, high voltage roentgen therapy seemed to lessen the swelling and decrease the pain for several months. There was no proof that irradiation prolonged life or cured the disease.

Sarcoma of the Knee Joint Resulting from Roentgenotherapy.—Sarcoma arising as a result of roentgenotherapy is rare clinically. Fifteen cases have been assembled from the literature. Becker [22] reports such a tumor in a 25 year old woman. At the age of 11, the patient was treated by roentgen irradiation for swelling of the knee, clinically diagnosed as tuberculosis. Tremendous overirradiation was adminis-

22. Becker, F. D.: Deutsche Ztschr. f. Chir. **248**:11, 1937.

tered by a nonmedical technician. Six months later atrophy of the skin appeared, together with a small swelling over the patella. This swelling soon subsided. Six years later the tumor appeared and grew rapidly, soon reaching the size of a fist. In 1932 the tumor was resected. Only chronic inflammation was reported. Clear small zones of atrophy were visible in the patella and the lower part of the femur. In 1935, two months after pregnancy, the patient returned with a marked increase of local symptoms and an obvious sarcoma of the lower end of the femur which proved on section to be of the chondro-fibro-osteoid variety. Metastases were present in the lung. The patient was still alive at the date of the report. These sarcomas arise four to eight years after irradiation. Most of the patients are young persons who have been overirradiated for tuberculosis. The prognosis is unfavorable. In most of the cases histologic examination has revealed a polymorphocellular or spindle cell sarcoma. Irradiation of the epiphysial zones may be a factor in bringing about this condition.

Synovioma.—Fehr [23] adds 4 more cases of synovial sarcoma to the 17 previously reported as such in the literature. Photographs and histologic sections are well reproduced. The author stresses the slow but sure malignancy of the lesion and emphasizes the difficulty encountered often in the pathologic identification of the tumor. Clefts in the tissue early in the history of the tumor usually make it possible to recognize the synovial origin. Sections taken in late stages of the disease may reveal purely sarcomatous structure. He advises in the early stages, when feasible, wide excision with the diathermy knife. If this cannot be accomplished with certainty, or if a recurrence has appeared, amputation must be performed. When metastases occur, the lungs are most often involved and the regional lymph nodes next often.

Osseous Metastases from Carcinoma of the Stomach.—Lawton [24] noted that 10 patients in a group of 606 with carcinoma of the stomach treated at the Presbyterian Hospital, Chicago, had pain which seemed to be of osseous origin but roentgenograms showed no skeletal metastases. Seven of these 10 patients died, and autopsies were performed. In 3 cases carcinomatous lesions were observed in section of the vertebrae and by microscopic study, although roentgenologic study of the involved bones showed no lesions. The author suggests that osseous metastases in carcinoma of the stomach may be more common than is usually thought since the lesions are not readily seen in roentgenograms.

THE KNEE

Pellegrini-Stieda Disease.—Pellegrini-Stieda disease, defined as a post-traumatic disorder of the knee characterized by opacities visible in

23. Fehr, A.: Beitr. z. klin. Chir. **165**:88, 1937.
24. Lawton, S. E.: Surgery **3**:121, 1938.

the roentgenogram near the internal condyle of the femur, usually cannot be demonstrated until two or three weeks after the injury. Cullen [25] states that the condition should be looked on not as a separate disease but as a local manifestation of post-traumatic changes common to joints. In support of this thesis he calls attention to the fact that the changes, though commonly affecting the tibial collateral ligament, may likewise occur in the tendons of attachment of the adductor magnus or vastus medialis muscle. They have points in common with traumatic myositis ossificans and the opacities of so-called subdeltoid bursitis. Since disagreement has arisen as to whether calcification or ossification is the true pathologic condition under discussion, the author points out that either of the processes may develop about joints after trauma. In the absence of trabeculation, he observes, it is impossible to differentiate the two conditions by the roentgenogram. The theory is advanced that a fatty degeneration may precede the calcific change, accounting for the delay in roentgenographic appearance. The final appearance of calcification or ossification may be related to glandular imbalance prevailing at the time in question.

Calcification of the Semilunar Cartilage.—Balensweig and Bosworth,[26] in reporting 2 cases of calcification of the semilunar cartilages of the knee joint, conclude that this lesion has its onset in middle life, may be bilateral, may occur without resulting in either objective or subjective symptoms and apparently is not caused by trauma. They advise operation when the lesion is complicated by cystic formation, or when the cartilage becomes loosened and gives rise to symptoms. Their first patient was a man 66 years of age who complained of pain and swelling on the outer aspect of the right knee. Examination showed a normal status except for arcus senilis of both eyes and the condition in the knee. The knee presented a flexion deformity of 30 degrees and localized swelling and tenderness over the external cartilage. Roentgenograms showed calcification of the external cartilage of both knee joints. Meniscectomy was done and the patient made a good symptomatic recovery. The second patient was a woman 44 years of age who complained of acute pain in the right knee. Examination showed a 5 degree flexion deformity and thickening and tenderness of the soft tissues of the joint. Roentgenograms revealed calcified meniscuses. At operation both cartilages were seen to contain calcium and were removed. The patient made a good symptomatic recovery. The proportions of uric acid and sugar in the blood were determined in the first case and were reported normal.

[ED. NOTE.—In the opinion of one of us this condition is not uncommon.]

25. Callen, H. S.: Radiology **29**:158, 1937.
26. Balensweig, I., and Bosworth, D. M.: Surgery **2**:120, 1937.

MISCELLANEOUS

Cystlike Cavities About the Shoulder Joint.—Morton and Fray [27] present examples of unusual roentgenologic appearances of the shoulder simulating cysts or giant cell tumors but in fact due to abnormal positions of the limb at the time of exposing the film. Fray [28] in the paper following gives an account of an investigation of the roentgenologic appearances of the shoulder with the arm in various positions. He finds that a combination of internal rotation and forward flexion produces typical cystlike shadows with great regularity. These shadows are cast by the articular margin of the head of the humerus. Other factors which contribute to or accentuate these appearances are atrophy of the bone and degenerative changes at the articular margins, with or without hypertrophic changes, the latter tending to accentuate the margin of the cystlike shadow. For routine roentgenologic examination of the shoulder, the placing of the arm in the anatomic position with the palm of the hand forward in the supinated position is recommended whenever external rotation can be employed. This defines the bony structures with great clarity and avoids the possibility of the production of confusing shadows.

Ossification of the Achilles Tendon—Hufnagel [29] reports a case of intratendinous ossification of the achilles tendon and discusses the various theories of calcification in soft tissue. His patient was a man 51 years of age who at the age of 9 suffered a complete rupture of the achilles tendon. He was treated conservatively and made a good symptomatic recovery. At 48, he suffered a contusion of the achilles tendon with subsequent pain in the tendon. Roentgenologic examination revealed three separate shadows of calcification in the tendon. The calcified area of the tendon was excised and its continuity restored by repairing with fascia lata. No connection of the calcified areas with either the tibia or the os calcis could be established. Histologic examination of the specimen revealed intratendinous areas of calcification and hyaline degeneration. The author explained this occurrence of calcium by hyaline degeneration with metaplasia of the connective tissue and subsequent deposition of calcium.

Dorsal and Plantar Flexion at Chopart's Joint.—Measurement of the flexion at Chopart's joint in 5 patients with ankylosis of the ankle joint demonstrated ranges of dorsiflexion up to an angle of 80 degrees and ranges of plantar flexion to a maximum angle of 125 degrees, in short, ranges of motion amounting to from 20 to 45 degrees in Chopart's joint (astragaloscaphoid and calcaneocuboid joints). Despite the common

27. Morton, J. J., and Fray, W. W.: Radiology **28**:668, 1937.
28. Fray, W. W.: Radiology **28**:673, 1937.
29. Hufnagel, H.: München. med. Wchnschr. **84**:1410, 1937.

teaching that normally 20 degree plantar-dorsal flexion is present in Chopart's joint, Zimmerman,[30] who tested some children and adults by attempted plantar immobilization of the hindpart of the foot, reports that children show 10 to 15 degrees of such motion and adults 5 degrees. The increased ranges in feet with ankylosis at the ankle joint was a compensatory development.

Gas Gangrene Treated With Sulfanilamide.—Bohlman[31] reported 3 cases of gas gangrene treated with sulfanilamide. The patients had prophylactic doses of a combined gas bacillus antitoxin. All responded promptly to sulfanilamide. Pending further study the author's conclusions were: 1. Conservative surgical principles should be combined with the use of the drug. 2. Sulfanilamide probably had a specific effect on gas bacilli, but the results may have been due to its checking symbiotic growth of streptococci.

ORTHOPEDIC OPERATIONS

Shelving Operation for Dislocated Hips.—Smith[32] carefully analyzes 67 cases of congenital dislocation of the hip. He concludes that patients with untreated unilateral dislocations have a good chance of reaching the age of 15 without symptoms, but that it is unlikely that they will reach the age of 40 without being forced to seek medical aid. Patients with bilateral dislocation of the hips complain of pain or fatigue before the age of 10 and cannot be expected to reach 20 without disability. The shelving operation has proved successful in ameliorating symptoms, especially if performed after the age of 10 and if the condition was unilateral. In younger patients the results were poor.

Femoral Bifurcation With the Aid of the Trochanter Minor.—In cases of irreducible old congenital dislocation of the hip in which the lesser trochanter is opposite the region of the original acetabulum, Hass[33] performs a transverse osteotomy below the lesser trochanter in order to get this trochanter to rest against the acetabulum. This is possible in all cases of forward, lateral or intermediate dislocation. It is a modification of the osteotomy which has given the author a stable painless hip. He differentiates it from the level advised by Lance as being aimed at getting the lesser trochanter into the acetabulum, whereas Lance tries to implant the femur itself below the lesser trochanter into the original socket.

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30. Zimmerman, M.: Ztschr. f. Orthop. **66**:21, 1937.

31. Bohlman, H. R.: Gas Gangrene Treated with Sulfanilamide: Report of Three Cases, J. A. M. A. **109**:254 (July 24) 1937.

32. Smith, A. R.: Ann. Surg. **106**:92, 1937.

33. Hass, J.: Ztschr. f. Orthop. **66**:353, 1937.

Operative Correction of Congenital Coxa Vara.—Sorrell [34] reviews the theories of the cause of congenital coxa vara and the commonly accepted methods of treament. He describes a new operative procedure for the correction of this deformity. It consists of a wedge-shaped osteotomy of the femoral neck just beyond the greater trochanter, with the base of the wedge upward. The wedge-shaped piece of bone is placed in a reversed position between the osteotomized ends of the femoral neck so that the base of the wedge is downward. Before the operation, tracings and measurements are made on the roentgenogram. By a wedge with an angulation of 20 degrees a correction of 40 degrees can be obtained in the deformity. The femoral neck is exposed by an anterior incision just medial to the greater trochanter.

Hallux Valgus.—Hendrix and Kempeneers [35] review the pathologic changes and the operative procedures which have been used in the treatment of hallux valgus. A satisfactory operation should: (1) correct the abduction and rotation of the great toe, (2) bring the first metatarsal into a position parallel to the second, (3) reestablish muscular equilibrium and (4) correct the spread of the arch anteriorly and longitudinally. The author's feel that of all of the operative procedures that of Holimann, a cuneiform osteotomy of the first metatarsal head, correcting the metatarsus varus is most effective. Not all patients with hallux valgus require operation. The authors have noted that a support and correction of the weakness of the musculature is adequate for milder deformities.

Fascial Transplants in Paralysis About the Spine.—A report of an attempt to study and apply the pioneer work of Lowman with fascial transplants is made by Dickson,[36] who bases his observations on 44 cases with weaknesses of the following muscles: superior rectus, 1; inferior rectus, 11; upper oblique, 7; lower oblique, 26; quadratus lumborium, 8, and various combinations of these. Fascial transplants about the shoulder for the purpose of stabilizing the scapula and thus preventing deformity of the chest and cervical region and improving the function of the muscles in the upper extremity are discussed. They have proved useful for two types of condition: (1) paralytic scoliosis with drop shoulders and marked cervical curvature and (2) paralysis of the scapular muscles with asymmetry of the shoulder, deficient stability of the shoulder girdle and a high thoracic curve. The procedure for correcting paralytic scoliosis with cervical curvature was carried out in 6 cases and proved satisfactory beyond expectations. In all cases the shoulders remained elevated to a satisfactory degree and no support was necessary. The procedure to correct paralysis of the

34. Sorrell, E.: Mém. Acad. de chir., Paris **63**:739, 1937.
35. Hendrix and Kempeneers: Bull. Soc. d'orthop. **9**:17, 1937.
36. Dickson, F. D.: J. Bone & Joint Surg. **19**:405, 1937

scapular muscles was carried out in 2 cases, 1 of which is old enough for a report. After three years practically normal use of the arm and shoulder has been restored with no increase in lateral deformity of the upper thoracic part of the spine. Line drawings and photographs are given.

FRACTURES

Faultily United Colles Fracture.—Campbell [37] reports a new operation to correct the deformities due to malunion of Colles fractures. Shortening of the radius, angulation of the radial articular surface and prominence of the styloid process of the ulna are all corrected, whereas procedures such as radial osteotomy or resection of the lower end of the ulna correct only one or two of the deforming elements. The operation consists of osteotomy of the radius with insertion at the site of osteotomy of a pyramidal wedge of bone taken from the lower end of the ulna. This procedure has been carried out in 19 cases; 11 of the 12 known end results were excellent.

Dislocation of the Semilunar Bone.—In general, dislocations of the semilunar bones should be reduced if at all possible. Open reduction is possible three, four or even six weeks after displacement. Nell [38] reports that Böhler, using mechanical distraction at open operation in one case, reduced a six month old dislocation. As a rule the end results are good in these reduced dislocations of the semilunar bones. Fractures of the semilunar bones rarely form pseudoarthroses and operative excision is indicated only rarely, in cases of comminuted fractures. Long fixation may be required. Extirpation is reserved for malacia of the semilunar bones which has been treated for at least six months by efficient rest without success. If arthritis deformans is visible on the roentgenogram, it is too late to operate, since the function will not be improved or the pain lessened. To spare the remaining important ligaments of the wrist the author advocates the palmar incision. The dorsal incision, while easier to perform, injures many ligaments and later results in serious carpal disturbances. It is difficult to avoid traumatizing the adjacent cartilages of the joint through this incision, since extensive stripping is required. A curved tenotome helps to free the bone at operation, dividing only the ligaments which are attached to the semilunar bone. A 5 to 6 cm. longitudinal incision is used, commencing 1 cm. above the pisiform bone. The median nerve and the flexor muscles of the fingers are retracted toward the ulna.

Fractures of the Terminal Phalanxes.—Perschl [39] discusses small fractures of the tip of the terminal phalanxes. These are often caused

37. Campbell, W. C.: Malunited Colles' Fractures, J. A. M. A. **109**:1105 (Oct. 2) 1937.

38. Nell, W.: Beitr. z. klin. Chir. **165**:619, 1937.

39. Perschl, A.: München. med. Wchnschr. **84**:810, 1937.

by a blow from a hammer and characterized by subungual hematoma, swelling and pain. Roentgenograms reveal a small fracture of the tip of the phalanx. Treatment consists of draining the subungual hematoma and splinting the finger. Patients are free from symptoms in about four weeks, and after six weeks the roentgenogram may show a slight diminution in the width of the line of fracture. It takes four to six months for these fractures to appear healed in the roentgenogram.

Fractures in Paget's Disease.—Taveriner and Losserre [40] express the opinion that fractures occur in Paget's disease more commonly than has been thought. They report 7 cases in which fracture occurred in Paget's disease. Four of the fractures were in eburnated bone and 3 were in areas of sarcomatous degeneration. Fracture rarely occurs during the early stages of the disease. It takes place most commonly when the bone appears very dense on roentgenologic examination but little increased in size. These eburnated bones break at the sites where fractures most commonly occur. Insignificant trauma is required in repairing these fractures. The bones usually consolidate rapidly without complications. Later in the disease fractures may occur in places where there is marked decalcification or sarcomatous alteration. In one instance the authors were able to study the histologic structure of the fractured eburnated bone. It was twice as rich in minerals as a normal bone and resembled ivory in texture. No great alteration in trabecular structure was observed.

RESEARCH

Destruction by Use in the Human Body.—Meyer [41] lists a large number of pathologic changes observed in the dissecting room as chronic kinetic lesions. He finds that the supporting tissues of the body may be weakened or severed by the attrition accompanying ordinary routine movements in the course of daily life. He lists among such changes: (1) fraying and destruction of the walls of the bursa; (2) fraying of the articular capsules; (3) defects of the articular capsule; (4) destruction of ligaments; (5) fraying of muscles; (6) fraying and partial division of tendons; (7) dislocation of tendons; (8) destruction of fibrocartilages; (9) destruction of hyaline articular cartilage; (10) fissuring of the intervertebral disks; (11) erosion of bone; (12) rupture of tendons; (13) formation of bony excrescences. These changes were more extensive in the case of persons engaged in laborious occupations. There was little tendency to heal, as destructive processes greatly exceeded those of healing.

40. Taveriner, L., and Losserre, C.: Rev. d'orthop. **24**:569, 1937.

41. Meyer, A. W.: California & West. Med. **47**:375, 1937.

Experimental Sprains in the Joints.—Miltner and his co-workers [42] in the study of sprains in the joints were able to produce manually mild and severe forms of sprain in the knee joints of rabbits. After the trauma the joints were examined roentgenologically to exclude the possibility of fracture and subsequently representative animals were killed at weekly intervals and the gross and microscopic effects of the injury studied. These experiments showed that trauma applied to joints causes an acute inflammatory reaction at the points of greatest injury. In severe injury the bony or cartilaginous structures may be involved. In 12 rabbits mild sprains were produced, and necropsies were performed weekly to the sixth week. The trauma caused an acute inflammatory reaction with exudation of synovial fluid, edema of the subsynovial and periarticular connective tissues and moderate fibroblastic proliferation and leukocytic infiltration. Gross evidence and external signs of pathologic change disappeared by the fourth week, but microscopic evidence of inflammation, slight edema and fibrosis persisted until the sixth week. Hence it was suggested that the joint should be protected for at least two weeks after the clinical signs have disappeared.

On the 11 rabbits with severe sprains autopsies were done from one to eleven weeks later. There was inflammatory reaction of the soft tissues similar to the changes seen in the first group but more severe. These changes in the soft tissue persisted to the eighth week and gradually resolved during the next two weeks. In addition to the changes noted in the first group, detached bits of bone too small to cast shadows in roentgenograms were usually seen at the ligamentous-osseous junction. A degeneration of the cells also was observed in the intermediate zone of hyaline cartilage of the tibia on the side of the joint opposite to the sprained ligaments. In one case a traumatic fissure in this intermediate zone of cartilage was noted. It is thought that in this slow degeneration of cartilage may lie one of the causes for chronic traumatic arthritis.

Pathologic Study of Tendons.—Günther,[43] in a study of pathologic material from fascia, tendons and ligaments, concludes that tendons and ligaments may be affected by diseases and inflammatory conditions much as is a bursa. He shows the progressive nature of changes in ligamentous structures: inflammation of the ligamentous structures, changes in the proliferation of the fibers of connective tissue and hyaline degeneration. He traces the development of Dupuytren's contracture and the formation of tumors from simpler pathologic alterations.

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42. Miltner, L. J.; Hu, C. H., and Fang, H. C.: Experimental Joint Sprain: Pathologic Study, Arch. Surg. **35**:234 (Aug.) 1937.

43. Günther, G. E.: Beitr. z. klin. Chir. **166**:32, 1937.